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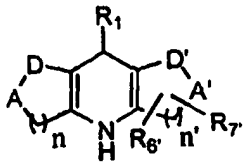
(54) Title: DIHYDROPYRIDINE COMPOUNDS AND METHODS OF USE

(57) Abstract

Compounds having formula (I) are useful in treating diseases prevented by or ameliorated with potassium channel openers. Also disclosed are potassium channel opening compositions and a method of opening potassium channels in a mammal.



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DIHYDROPYRIDINE COMPOUNDS AND METHODS OF USE

This application is a continuation-in-part of US application serial number 09/181,239, filed October 28,1998, incorporated herein by reference.

TECHNICAL FIELD

Novel dihydropyridine compounds and their derivatives can open potassium channels and are useful for treating a variety of medical conditions.

BACKGROUND OF INVENTION

Potassium channels play an important role in regulating cell membrane excitability. When the potassium channels open, changes in the electrical potential across the cell membrane occur and result in a more polarized state. A number of diseases or conditions can be treated with therapeutic agents that open potassium channels; see (K. Lawson, Pharmacol. Ther., v. 70, pp. 39-63 (1996)); (D.R. Gehlert et al., Prog. Neuro-Psychopharmacol & Biol. Psychiat., v. 18, pp. 1093-1102 (1994)); (M. Gopalakrishnan et al., Drug Development Research, v. 28, pp. 95-127 (1993)); (J.E. Freedman et al., The Neuroscientist, v. 2, pp. 145-152 (1996)); (D. E. Nurse et al., Br. J. Urol., v. 68 pp. 27-31 (1991)); (B. B. Howe et al., J. Pharmacol. Exp. Ther., v. 274 pp. 884-890 (1995)); and (D. Spanswick et al., Nature, v. 390 pp. 521-25 (December 4, 1997)). Such diseases or conditions include asthma, epilepsy, hypertension, male sexual dysfunction, female sexual dysfunction, migraine, pain, urinary incontinence, stroke, Raynaud's Syndrome, eating disorders, functional bowel disorders, and neurodegeneration.

Potassium channel openers also act as smooth muscle relaxants. Because urinary incontinence can result from the spontaneous, uncontrolled contractions of the smooth muscle of the bladder, the ability of potassium channel openers to hyperpolarize bladder cells and relax bladder smooth muscle provides a method to ameliorate or prevent urinary incontinence.

WO 9408966, EP 0539153 A1 and EP 0539154 A1 disclose a group of acridinedione and quinolone compounds that belong to the larger general chemical class of dihydropyridines.

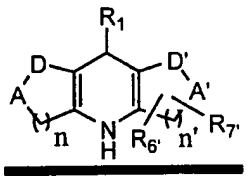
Dihydropyridines of differing chemical structure may possess a variety of biological activities. DE 3605742 A1 and US 4,284,634 disclose compounds that are calcium channel antagonists.

US 5,025,011 discloses pyridine compounds as possessing both calcium channel and β-receptor blocking activity while EP 299727 discloses compounds that act as platelet activating factor (PAF) antagonists.

Compounds of the present invention are novel, hyperpolarize cell membranes, open potassium channels, relax smooth muscle cells, inhibit bladder contractions and are useful for treating diseases that can be ameliorated by opening potassium channels.

SUMMARY OF THE INVENTION

In its principle embodiment, the present invention discloses compounds having formula I:



I,

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof, wherein

n and n' are independently 1-3;

A is selected from O, $-NR_2$, and S;

A' is selected from O, $-NR_{2'}$, S, and $CR_4R_{5'}$;

D is selected from CH_2 and C(O);

D' is selected from CH_2, C(O), S(O), and $S(O)_2$;

R_1 is selected from aryl and heterocycle;

R_2 and $R_{2'}$ are independently selected from hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, $-NZ_1Z_2$,

and (NZ_1Z_2)alkyl wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

R_4 and R_5 are independently selected from hydrogen and alkyl;

R_6 and R_7 are independently selected from hydrogen and alkyl;

with the proviso that when D is CH_2 then D' is other than CH_2;

with the proviso that when D' is S(O) or $S(O)_2$ then A' is CR_4R_5; and

with the proviso that the following compounds are excluded,

8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-2,6-dipropanoic acid,

(8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-2,6-ethyldipropanate,

8-[2-(difluoromethoxy)phenyl]-6-methyl-4,5,6,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,4-e]pyridine-1,7(3H)-dione,

8-[2-(difluoromethoxy)phenyl]-2,6-dimethyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

2,6-dimethyl-8-phenyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

8-(3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2,4-dichlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-methoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-iodophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-phenyl-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-aminophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[2-(difluoromethoxy)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2,3,4-trimethoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[2-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-chloro-3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

3,7-dimethyl-10-phenyl-3,4,5,6,7,10-hexahydro-1H,9H-dipyrano[4,3-b:3,4-e]pyridine-1,9-dione,

6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(1,3-benzodioxol-5-yl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(3-methoxyphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(2-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

6,6-dimethyl-9-(2-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

6,6-dimethyl-9-[2-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione, and

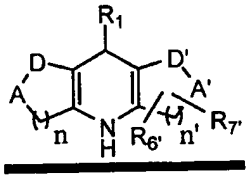
9-[3-(benzyloxy)phenyl]-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione.

DETAILED DESCRIPTION OF THE INVENTION

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use of the invention, may be made without departing from the spirit and scope thereof.

In its principle embodiment, the present invention discloses compounds having formula I:



I,

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof, wherein

n and n' are independently 1-3;

A is selected from O, $-NR_2$, and S;

A' is selected from O, $-NR_{2'}$, S, and $CR_{4'}R_{5'}$;

D is selected from CH_2 and C(O);

D' is selected from CH_2, C(O), S(O), and $S(O)_2$;

R_1 is selected from aryl and heterocycle;

R_2 and $R_{2'}$ are independently selected from hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, $-NZ_1Z_2$, and (NZ_1Z_2)alkyl wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

$R_{4'}$ and $R_{5'}$ are independently selected from hydrogen and alkyl;

R_6 and R_7 are independently selected from hydrogen and alkyl;

with the proviso that when D is CH_2 then D' is other than CH_2;

with the proviso that when D' is S(O) or $S(O)_2$ then A' is CR_4R_5; and

with the proviso that the following compounds are excluded,

8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-2,6-dipropanoic acid,

(8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-2,6-ethyldipropanate,

8-[2-(difluoromethoxy)phenyl]-6-methyl-4,5,6,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,4-e]pyridine-1,7(3H)-dione,

8-[2-(difluoromethoxy)phenyl]-2,6-dimethyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

2,6-dimethyl-8-phenyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

8-(3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2,4-dichlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-methoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-iodophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-phenyl-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-aminophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[2-(difluoromethoxy)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2,3,4-trimethoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[2-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-chloro-3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

3,7-dimethyl-10-phenyl-3,4,5,6,7,10-hexahydro-1H,9H-dipyrano[4,3-b:3,4-e]pyridine-1,9-dione,

6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(1,3-benzodioxol-5-yl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(3-methoxyphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

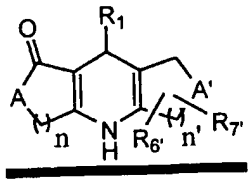
9-(2-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

6,6-dimethyl-9-(2-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

6,6-dimethyl-9-[2-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione, and

9-[3-(benzyloxy)phenyl]-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione.

In another embodiment, the present invention discloses compounds having formula II:



II,

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, n, n', A, A', R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is NR_2; A' is $NR_{2'}$; n' is 1; and n, R_1, R_2, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is NR_2; A' is O; n' is 1; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is NR_2; A' is S; n' is 1; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 1; and n, R_1, R_2, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is O; A' is $NR_{2'}$; n' is 1; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is O; A' is O; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is O; A' is S; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is S; A' is $NR_{2'}$; n' is 1; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is S; A' is O; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is S; A' is S; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is S; A' is $CR_{4'}R_{5'}$; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is NR_2; A' is $NR_{2'}$; n' is 2; and n, R_1, R_2, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is NR_2; A' is O; n' is 2; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is NR_2; A' is S; n' is 2; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is O; A' is $NR_{2'}$; n' is 2; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is O; A' is O; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is O; A' is S; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

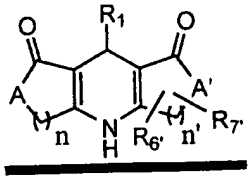
In another embodiment of the present invention, compounds have formula II wherein, A is S; A' is $NR_{2'}$; n' is 2; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is S; A' is O; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is S; A' is S; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is S; A' is $CR_{4'}R_{5'}$; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment, the present invention discloses compounds having formula III:



III,

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, n, n', A, A', R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $NR_{2'}$; n' is 1; and n, R_1, R_2, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $NR_{2'}$; n' is 1; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, R_2, and $R_{2'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is O; n' is 1; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is O; n' is 1; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1 and R_2 are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is S; n' is 1; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 1; and n, R_1, R_2, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 1; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, R_2, $R_{4'}$, and $R_{5'}$, are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 1; n is 2; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, R_2, $R_{4'}$, and $R_{5'}$, are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $NR_{2'}$; n' is 1; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is O; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is O; n' is 1; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1 is as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is S; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 1; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, $R_{4'}$, and $R_{5'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 1; n is 2; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, $R_{4'}$, and $R_{5'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is S; A' is $NR_{2'}$; n' is 1; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is S; A' is O; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is S; A' is S; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is S; A' is $CR_{4'}R_{5'}$; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $NR_{2'}$; n' is 2; and n, R_1, R_2, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $NR_{2'}$; n' is 2; n is 2; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, R_2, and $R_{2'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is O; n' is 2; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is S; n' is 2; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 2; and n, R_1, R_2, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 2; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, R_2, $R_{4'}$, and $R_{5'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 2; n is 2; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, R_2, $R_{4'}$, and $R_{5'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $NR_{2'}$; n' is 2; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is O; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is S; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 2; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, $R_{4'}$, and $R_{5'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 2; n is 1; $R_{4'}$ is hydrogen; $R_{5'}$ is hydrogen; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1 is as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 2; n is 1; $R_{4'}$ is methyl; $R_{5'}$ is methyl; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1 is as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 2; n is 2; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, $R_{4'}$, and $R_{5'}$ are as defined in formula I.

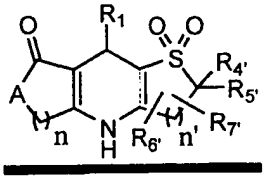
In another embodiment of the present invention, compounds have formula III wherein, A is S; A' is $NR_{2'}$; n' is 2; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is S; A' is O; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is S; A' is S; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is S; A' is $CR_{4'}R_{5'}$; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment, the present invention discloses compounds having formula IV:



IV,

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, n, n', A, R_1, $R_{4'}$ and $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is NR_2; n' is 1; and n, R_1, R_2, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is NR_2; n' is 1; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, R_2, $R_{4'}$, and $R_{5'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is NR_2; n' is 1; n is 2; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; R_1, R_2, $R_{4'}$, $R_{5'}$, are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is O; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is S; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is NR_2; n' is 2; and n, R_1, R_2, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

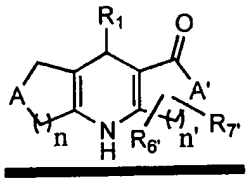
In another embodiment of the present invention, compounds have formula IV wherein, A is NR_2; n' is 2; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, R_2, $R_{4'}$, and $R_{5'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is O; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is O; n' is 2; n is 1; $R_{6'}$ is hydrogen; $R_{7'}$ is hydrogen; and R_1, $R_{4'}$, and $R_{5'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is S; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment, the present invention discloses compounds having formula V:



V,

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, n, n', A, A', R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR_2; A' is $NR_{2'}$; n' is 1; and n, R_1, R_2, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR_2; A' is O; n' is 1; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR_2; A' is S; n' is 1; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 1; and n, R_1, R_2, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is $NR_{2'}$; n' is 1; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is O; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is S; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is $NR_{2'}$; n' is 1; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is O; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is S; n' is 1; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is $CR_{4'}R_{5'}$; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR_2; A' is $NR_{2'}$; n' is 2; and n, R_1, R_2, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR_2; A' is O; n' is 2; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR_2; A' is S; n' is 2; and n, R_1, R_2, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR_2; A' is $CR_{4'}R_{5'}$; n' is 2; and n, R_1, R_2, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is $NR_{2'}$; n' is 2; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is O; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is S; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is $CR_{4'}R_{5'}$; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

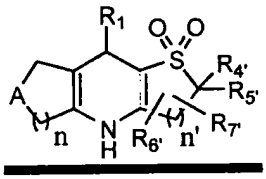
In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is $NR_{2'}$; n' is 2; and n, R_1, $R_{2'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is O; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is S; n' is 2; and n, R_1, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is $CR_{4'}R_{5'}$; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment, the present invention discloses compounds having formula VI:



VI,

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, n, n', A, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is NR_2; n' is 1; and n, R_1, R_2, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is O; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is S; n' is 1; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is NR_2; n' is 2; and n, R_1, R_2, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is O; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is S; n' is 2; and n, R_1, $R_{4'}$, $R_{5'}$, $R_{6'}$, and $R_{7'}$ are as defined in formula I.

Another embodiment of the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I-

VI or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof in combination with a pharmaceutically acceptable carrier.

Yet another embodiment of the invention relates to a method of treating hypertension comprising administering a therapeutically effective amount of a compound of formula I-VI or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Yet another embodiment of the invention relates to a method of treating asthma, epilepsy, hypertension, Raynaud's syndrome, migraine, pain, eating disorders, urinary incontinence, functional bowel disorders, neurodegeneration, stroke, female sexual dysfunction including, but not limited to, female anorgasmia, clitoral erectile insufficiency, vaginal engorgement, dyspareunia, and vaginismus, and male sexual dysfunction including, but not limited to, male erectile dysfunction and premature ejaculation comprising administering a therapeutically effective amount of a compound of formula I-VI including 8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-2,6-dipropanoic acid; (8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-2,6-ethyldipropanate; 8-[2-(difluoromethoxy)phenyl]-6-methyl-4,5,6,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,4-e]pyridine-1,7(3H)-dione; 8-[2-(difluoromethoxy)phenyl]-2,6-dimethyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione; 2,6-dimethyl-8-phenyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione; 8-(3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(2,4-dichlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(4-methoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(4-iodophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(4-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(3-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(2-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-phenyl-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(2-aminophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-[2-(difluoromethoxy)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(2-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(2,3,4-trimethoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-

b:3,4-e]pyridine-1,7(4H)-dione; 8-[2-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(2-chloro-3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(4-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(4-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(3-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 8-(2-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione; 3,7-dimethyl-10-phenyl-3,4,5,6,7,10-hexahydro-1H,9H-dipyrano[4,3-b:3,4-e]pyridine-1,9-dione; 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione; 9-(1,3-benzodioxol-5-yl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione; 9-(3-methoxyphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione; 9-(2-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione; 6,6-dimethyl-9-(2-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione; 6,6-dimethyl-9-[2-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione; and 9-[3-(benzyloxy)phenyl]-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Definition of Terms

The term "alkenyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl and the like.

The term "alkoxy," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy and the like.

The term "alkoxyalkoxy," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through another alkoxy group, as defined

herein. Representative examples of alkoxyalkoxy include, but are not limited to, tert-butoxymethoxy, 2-ethoxyethoxy, 2-methoxyethoxy, methoxymethoxy, and the like.

The term "alkoxyalkoxyalkyl," as used herein, refers to an alkoxyalkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkoxyalkyl include, but are not limited to, tert-butoxymethoxymethyl, ethoxymethoxymethyl, (2-methoxyethoxy)methyl, 2-(2-methoxyethoxy)ethyl, and the like.

The term "alkoxyalkyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkyl include, but are not limited to, tert-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, methoxymethyl, and the like.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, and the like.

The term "alkoxycarbonylalkyl," as used herein, refers to an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxycarbonylalkyl include, but are not limited to, 3-methoxycarbonylpropyl, 4-ethoxycarbonylbutyl, 2-tert-butoxycarbonylethyl, and the like.

The term "alkyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like.

The term "alkylcarbonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, 1-oxopentyl, and the like.

The term "alkylcarbonylalkyl," as used herein, refers to an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylcarbonylalkyl include, but are not limited to, 2-oxopropyl, 3,3-dimethyl-2-oxopropyl, 3-oxobutyl, 3-oxopentyl, and the like.

The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, tert-butylcarbonyloxy, and the like.

The term "alkylsulfinyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfinyl group, as defined herein. Representative examples of alkylsulfinyl include, but are not limited, methylsulfinyl, ethylsulfinyl, and the like.

The term "alkylsulfonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkylsulfonyl include, but are not limited, methylsulfonyl, ethylsulfonyl, and the like.

The term "alkylthio," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkylthio include, but are not limited, methylsulfanyl, ethylsulfanyl, tert-butylsulfanyl, hexylsulfanyl, and the like.

The term "alkynyl," as used herein, refers to a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, 1-butynyl and the like.

The term "aryl," as used herein, refers to a monocyclic carbocyclic ring system or a bicyclic carbocyclic fused ring system having one or more aromatic rings. Representative examples of aryl include, azulenyl, indanyl, indenyl, naphthyl, phenyl, tetrahydronaphthyl, and the like.

The aryl groups of this invention can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, aryl, azido, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, formyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, mercapto, nitro, sulfo, sulfonate, $-NR_{80}R_{81}$ (wherein, R_{80} and R_{81} are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl and formyl), and $-C(O)NR_{82}R_{83}$ (wherein, R_{82} and R_{83} are independently selected from hydrogen, alkyl, aryl, and arylalkyl).

The term "arylalkoxy," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of arylalkoxy include, but are not limited to, 2-phenylethoxy, 3-naphth-2-ylpropoxy, 5-phenylpentyloxy, and the like.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylalkoxycarbonyl include, but are not limited to, benzyloxycarbonyl, naphth-2-ylmethoxycarbonyl, and the like.

The term "arylalkyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-naphth-2-ylethyl, and the like.

The term "arylcarbonyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylcarbonyl include, but are not limited to, benzoyl, naphthoyl, and the like.

The term "aryloxy," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of aryloxy include, but are not limited to, phenoxy, naphthyloxy, 3-bromophenoxy, 4-chlorophenoxy, 4-methylphenoxy, 3,5-dimethoxyphenoxy, and the like.

The term "aryloxyalkyl," as used herein, refers to an aryloxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of aryloxyalkyl include, but are not limited to, 2-phenoxyethyl, 3-naphth-2-yloxypropyl, 3-bromophenoxymethyl, and the like.

The term "azido," as used herein, refers to a $-N_3$ group.

The term "carbonyl," as used herein, refers to a -C(O)- group.

The term "carboxy," as used herein, refers to a $-CO_2H$ group.

The term "carboxyalkyl," as used herein, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of carboxyalkyl include, but are not limited to, carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, and the like.

The term "cyano," as used herein, refers to a -CN group.

The term "cyanoalkyl," as used herein, refers to a cyano group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cyanoalkyl include, but are not limited to, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, and the like.

The term "cycloalkyl," as used herein, refers to a saturated cyclic hydrocarbon group containing from 3 to 8 carbons. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term "cycloalkylalkyl," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl and 4-cycloheptylbutyl, and the like.

The term "formyl," as used herein, refers to a -C(O)H group.

The term "halo" or "halogen," as used herein, refers to -Cl, -Br, -I or -F.

The term "haloalkoxy," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined

herein. Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2,2,2-trifluoroethoxy, trifluoromethoxy, pentafluoroethoxy, and the like.

The term "haloalkyl," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, 2-chloro-3-fluoropentyl, and the like.

The term "heterocycle," as used herein, refers to a monocyclic- or a bicyclic-ring system. Monocyclic ring systems are exemplified by any 5- or 6-membered ring containing 1, 2, 3, or 4 heteroatoms independently selected from oxygen, nitrogen and sulfur. The 5-membered ring has from 0-2 double bonds and the 6-membered ring has from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidine, azepine, aziridine, diazepine, 1,3-dioxolane, dioxane, dithiane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazoline, isothiazolidine, isoxazole, isoxazoline, isoxazolidine, morpholine, oxadiazole, oxadiazoline, oxadiazolidine, oxazole, oxazoline, oxazolidine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrimidine, pyridazine, pyrrole, pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrazine, tetrazole, thiadiazole, thiadiazoline, thiadiazolidine, thiazole, thiazoline, thiazolidine, thiophene, thiomorpholine, thiomorpholine sulfone, thiopyran, triazine, triazole, trithiane, and the like. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or another monocyclic ring system as defined herein. Representative examples of bicyclic ring systems include but are not limited to, for example, benzimidazole, benzothiazole, benzothiadiazole, benzothiophene, benzoxadiazole, benzoxazole, benzofuran, benzopyran, benzothiopyran, benzodioxine, 1,3-benzodioxole, cinnoline, indazole, indole, indoline, indolizine, naphthyridine, isobenzofuran, isobenzothiophene, isoindole, isoindoline, isoquinoline, phthalazine, pyranopyridine, quinoline, quinolizine, quinoxaline, quinazoline, tetrahydroisoquinoline, tetrahydroquinoline, thiopyranopyridine, and the like.

The heterocycle groups of this invention can be substituted with 1, 2,or 3 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl,

alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, aryl, azido, arylalkoxy, arylalkoxycarbonyl, arylalkyl, aryloxy, carboxy, cyano, formyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, mercapto, nitro, sulfo, sulfonate, $-NR_{80}R_{81}$ (wherein, R_{80} and R_{81} are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl and formyl), and $-C(O)NR_{82}R_{83}$ (wherein, R_{82} and R_{83} are independently selected from hydrogen, alkyl, aryl, and arylalkyl).

The term "heterocyclealkyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heterocyclealkyl include, but are not limited to, pyrid-3-ylmethyl, 2-pyrimidin-2-ylpropyl, and the like.

The term "hydroxy," as used herein, refers to an -OH group.

The term "hydroxyalkyl," as used herein, refers to a hydroxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-ethyl-4-hydroxyheptyl, and the like.

The term "lower alkyl," as used herein, refers to a straight or branched chain hydrocarbon group containing from 1-to-4 carbon atoms. Representative examples of lower alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, and the like.

The term "mercapto," as used herein, refers to a -SH group.

The term "nitro," as used herein, refers to a $-NO_2$ group.

The term "N-protecting group" or "nitrogen protecting group,"as used herein, refers to those groups intended to protect an amino group against undesirable reactions during synthetic procedures. N-protecting groups comprise carbamates, amides including those containing hetero arylgroups, N-alkyl derivatives, amino acetal derivatives, N-benzyl derivatives, imine derivatives, enamine derivatives and N-heteroatom derivatives. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, phenylsulfonyl, benzyl, triphenylmethyl (trityl), t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and the like. Commonly used N-protecting groups are disclosed in T.H. Greene and P.G.M.

Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), which is hereby incorporated by reference.

The term "-NZ_1Z_2," as used herein, refers to two groups, Z_1 and Z_2, which are appended to the parent molecular moiety through a nitrogen atom. Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl. Representative examples of -NZ_1Z_2 include, but are not limited to, amino, benzylamino, methylamino, acetylamino, acetylmethylamino, and the like.

The term "oxo," as used herein, refers to a =O moiety.

The term "oxy," as used herein, refers to a -O- moiety.

The term "sulfinyl," as used herein, refers to a -S(O)- group.

The term "sulfo," as used herein, refers to a -SO_3H group.

The term "sulfonate," as used herein, refers to -$S(O)_2OR_{96}$ group, wherein R_{96} is selected from alkyl, aryl, and arylalkyl, as defined herein.

The term "sulfonyl," as used herein, refers to a -SO_2- group.

The term "thio," as used herein, refers to a -S- moiety.

The term "pharmaceutically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. Prodrugs of the present invention may be rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in (T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987)).

The present invention contemplates pharmaceutically active metabolites formed by in vivo biotransformation of compounds of formula I-VI. The term pharmaceutically active metabolite, as used herein, refers to a compound formed by the in vivo biotransformation of compounds of formula I-VI. A thorough discussion of

biotransformation is provided in Goodman and Gilman's, The Pharmacological Basis of Therapeutics, seventh edition.

Compounds of the present invention may exist as stereoisomers wherein asymmetric or chiral centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral carbon atom. The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

Preferred compounds of formula I include, but are not limited to:

9-(4-chloro-3-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(3-methyl-4-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-[4-fluoro-3-(2-furyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(3-bromo-4-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(2,1,3-benzoxadiazol-5-yl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(3-bromo-4-chlorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-[3-bromo-4-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-[4-chloro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(4-bromo-3-chlorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(4-bromo-3-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(3-iodo-4-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-[3-nitro-4-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(5-bromo-4-fluoro-2-hydroxyphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-[3-chloro-4-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-[3-iodo-4-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(2,1,3-benzothiadiazol-5-yl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

8-(3,4-dibromophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(4-chloro-3-nitrophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(4-fluoro-3-iodophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(3-chloro-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(3,4-difluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(4-chloro-3-methylphenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(3-methyl-4-nitrophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-[4-fluoro-3-(2-furyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(3-bromo-4-methylphenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(2,1,3-benzoxadiazol-5-yl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(3-bromo-4-chlorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-[3-bromo-4-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-[4-chloro-3-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(4-bromo-3-chlorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(4-bromo-3-methylphenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(3-iodo-4-methylphenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-[3-nitro-4-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(5-bromo-4-fluoro-2-hydroxyphenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-[3-chloro-4-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

10-(3-bromo-4-fluorophenyl)-3,4,5,6,7,10-hexahydro-1H,9H-dipyrano[4,3-b:3,4-e]pyridine-1,9-dione,

9-(3-bromo-4-fluorophenyl)-4,5,6,9-tetrahydro-1H-furo[3,4-b]pyrano[3,4-e]pyridine-1,8(3H)-dione,

8-[3-iodo-4-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione, and

8-(2,1,3-benzothiadiazol-5-yl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

More preferred compounds of formula I include, but are not limited to:

8-(3-bromo-4-fluorophenyl)-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

8-(3-bromo-4-fluorophenyl)-2,6-dimethyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione,

8-(3-bromo-4-fluorophenyl)-2-ethyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione,

8-(3-bromo-4-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-(3-bromo-4-fluorophenyl)-2-(2-methoxyethyl)-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione,

9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

9-(3-bromo-4-fluorophenyl)-2-ethyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

8-(3-bromo-4-fluorophenyl)-2-[2-(4-morpholinyl)ethyl]-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione hydrochloride,

8-(3-bromo-4-fluorophenyl)-2-[2-(dimethylamino)ethyl]-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione hydrochloride,

9-(3-bromo-4-fluorophenyl)-2-(2-methoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9R)-9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9R)-9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

9-(3-cyanophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

8-(3-bromo-4-fluorophenyl)-6-methyl-2,3,4,5,6,8-hexahydro-7H-pyrrolo[3,4-b]thieno[2,3-e]pyridin-7-one 1,1-dioxide,

9-(3-bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydrobenzo[b][1,6]naphthyridine-1,9(2H,5H)-dione,

(9S)-9-(4-fluoro-3-iodophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydropyrido[4,3-b][1,6]naphthyridine-1,9(2H,5H)-dione,

9-(3-bromo-4-fluorophenyl)-7-methyl-3,4,5,6,7,9-hexahydropyrrolo[3,4-b]thiopyrano[2,3-e]pyridin-8(2H)-one 1,1-dioxide,

9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide,

(8R)-8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide,

(8S)-8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione,

(9R)-9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide,

9-(3-bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9R)-9-(3-bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-2-cyclopropyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-b][1,6]naphthyridin-8(4H)-one 1,1-dioxide,

(9R)-9-(4-fluoro-3-iodophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-(3-chloro-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(3-chloro-4-fluorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

9-[4-fluoro-3-(trifluoromethyl)phenyl]-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(4-chloro-3-fluorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(3,4-dichlorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-[4-chloro-3-(trifluoromethyl)phenyl]-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(3,4-dibromophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(3-cyanophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(5-chloro-2-thienyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(3-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(5-nitro-2-thienyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(5-nitro-3-thienyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-[4-fluoro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(4-chloro-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

8-[4-fluoro-3-(2-furyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

(8S)-8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

(8R)-8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

8-[4-fluoro-3-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

(9S)-9-[4-fluoro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-[4-fluoro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

8-(3,4-dichlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-methyl-3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

(9S)-9-(3,4-dibromophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-(3,4-dibromophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9S)-9-(4-methyl-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-(4-methyl-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9S)-9-(3,4-dichlorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-(3,4-dichlorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9S)-9-(4-chloro-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-(4-chloro-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9S)-9-(3,4-difluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-(3,4-difluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(8S)-8-(4-methyl-3-nitrophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

(8R)-8-(4-methyl-3-nitrophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

(8S)-8-(3,4-dichlorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

(8R)-8-(3,4-dichlorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

(8S)-8-[4-fluoro-3-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

(8R)-8-[4-fluoro-3-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,

(9S)-9-(3-bromo-4-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-(3-bromo-4-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

8-(3-chloro-4-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3,4-dibromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-bromo-4-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[4-chloro-3-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,4-e]pyridine-1,7(3H)-dione,

2-(2-aminoethyl)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

8-(4-bromo-3-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-fluoro-3-isopropenylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

(9S)-2-(2-aminoethyl)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

8-(3-iodo-4-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

(-) 9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(+) 9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

8-[3-(2-furyl)-4-methylphenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

9-(3-bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydrocyclopenta[b]pyrano[3,4-e]pyridine-1,8-dione,

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-1H-pyrano[4,3-b]quinoline-1,9(5H)-dione,

10-[4-fluoro-3-(trifluoromethyl)phenyl]-3,4,6,7,8,10-hexahydro-1H-pyrano[4,3-b]quinoline-1,9(5H)-dione, and

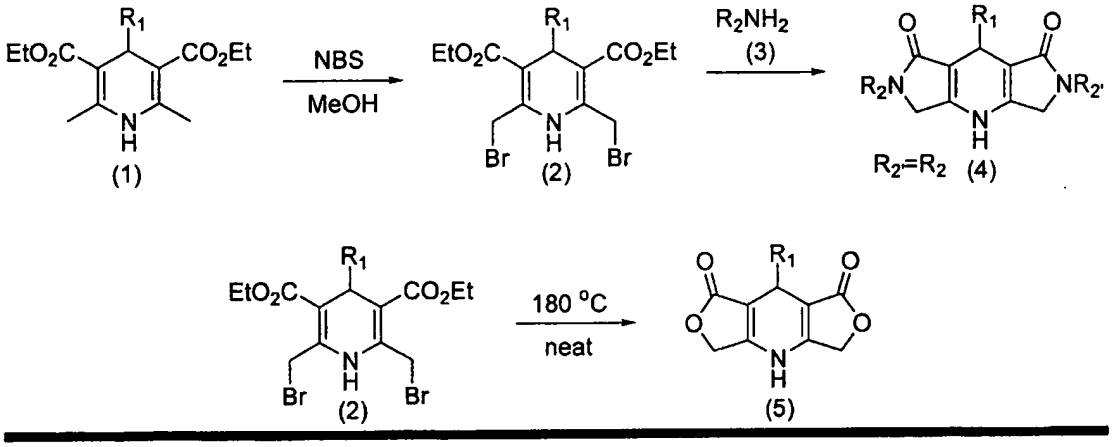
9-[4-fluoro-3-(trifluoromethyl)phenyl]-3,4,5,6,7,9-hexahydrocyclopenta[b]pyrano[3,4-e]pyridine-1,8-dione or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Preparation of Compounds of The Invention

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes and methods which illustrate a means by which the compounds of the invention can be prepared.

The compounds of this invention can be prepared by a variety of synthetic routes. Representative procedures are shown in Schemes 1-41.

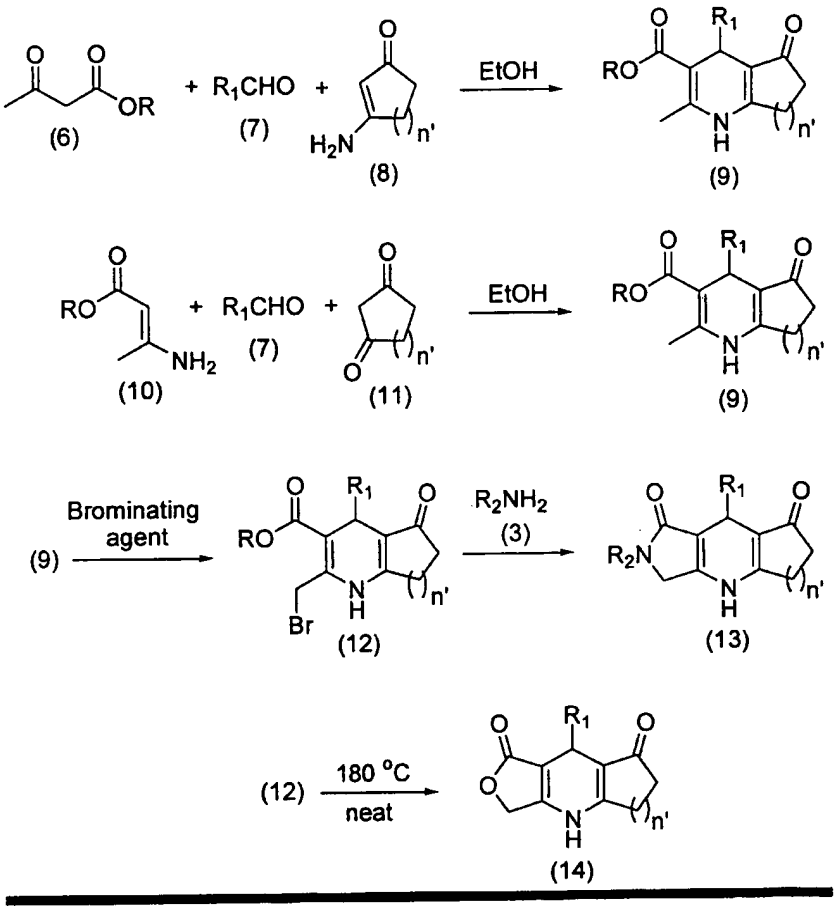
Scheme 1



Dihydropyridines of general formula (4), wherein R_2=$R_{2'}$ and R_1 and R_2 are as defined in formula I, can be prepared as described in Scheme 1. Diester (1), prepared by the Hantzsch reaction (Singer, A. And McElvain, S.M., Org. Synth., Coll. Vol. II (1943) 214), can be treated with with N-bromosuccinimide (NBS) to provide dibrominated dihydropyridine (2). Dibrominated dihydropyridine (2) can be treated with a primary amine (R_2NH_2) or ammonia in a protic solvent such as ethyl or methyl alcohol to provide dihydropyridines of general formula (4).

Dihydropyridines of general formula (5), wherein R_1 is as defined in formula I, can be prepared by heating dibromide (2) neat to 180 °C.

Scheme 2

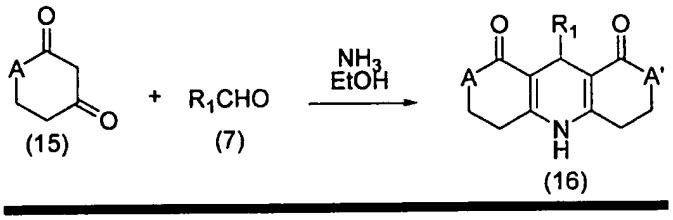


Dihydropyridines of the general formula (13), wherein R_1, R_2, and n' are as defined in formula I, can be prepared as described in Scheme 2. β-Keto esters of general formula (6), wherein R is lower alkyl, aldehydes of general formula (7), and cyclic enaminones of general formula (8) can be combined in ethanol with heat to provide dihydropyridines of general formula (9). Dihydropyridines of general formula (9) can be prepared using an alternate method. 3-Aminocrotonates of general formula (10), wherein R is lower alkyl, aldehydes of general formula (7), and cyclic dicarbonyls of general formula (11) can be combined and heated in ethanol to provide dihydropyridines of general formula (9). Dihydropyridines of general formula (9) can be treated with a brominating agent such as pyridinium tribromide in pyridine/chloroform or NBS in a solvent such as methanol, ethanol, isopropanol or chloroform to provide bromomethyl dihydropyridines of general formula (12). Bromomethyl dihydropyridines of general formula (12) can be treated with

a primary amine of general formula (3) in an alcoholic solvent to provide dihydropyridines of general formula (13).

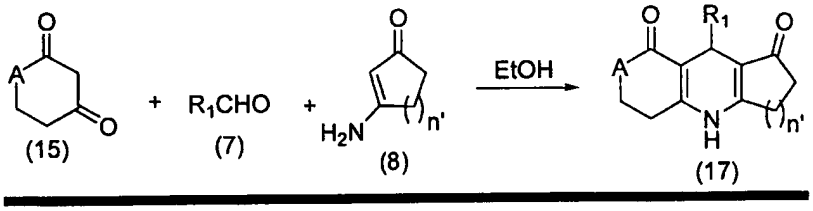
Dihydropyridines of general formula (14), wherein R_1 and n' are as defined in formula I, can be prepared by heating bromomethyl dihydropyridines of general formula (12) neat at 180 °C.

Scheme 3



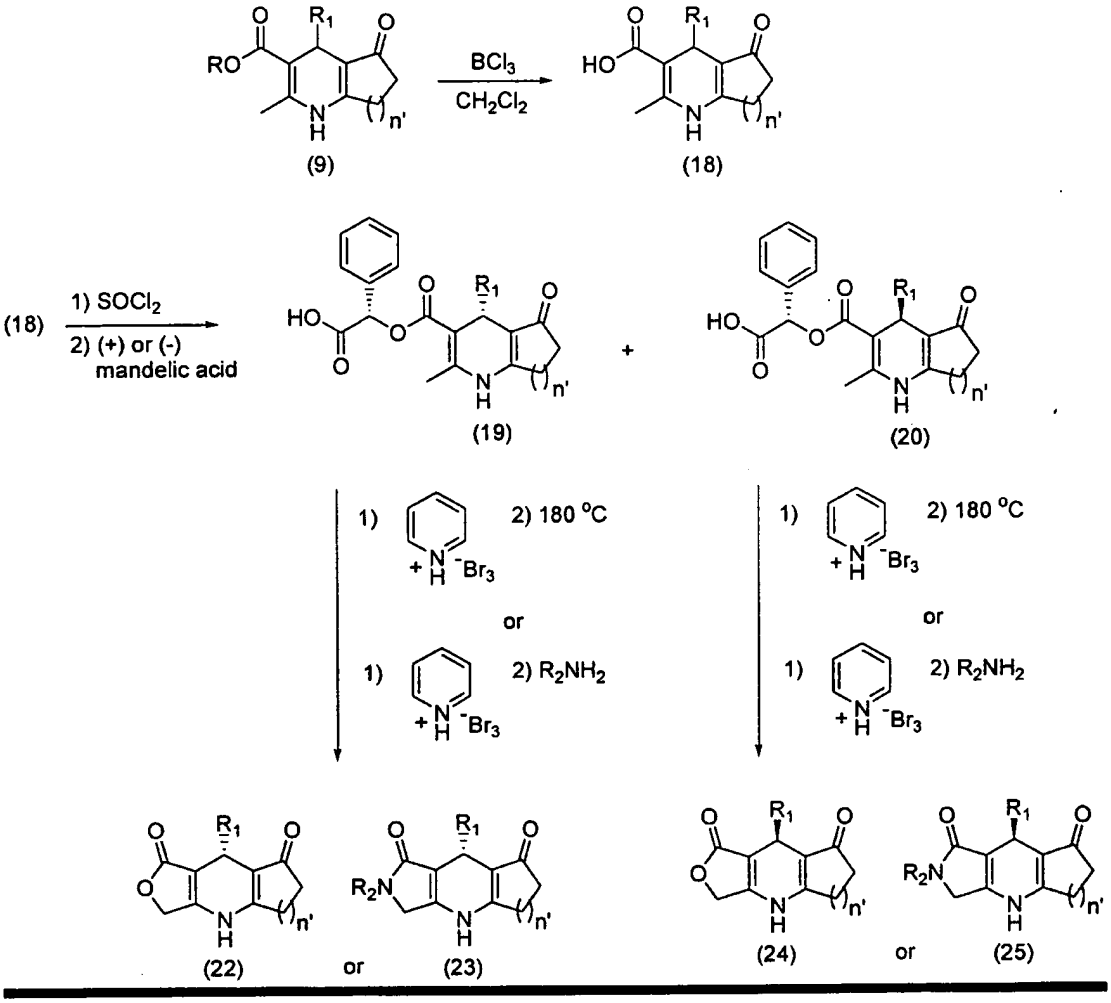
Dihydropyridines of the general formula (16), wherein A=A' and A is as defined in formula I, can be prepared as described in Scheme 3. Dicarbonyl compounds of general formula (15) can be treated with aldehydes of general formula (7) in ammonia and ethanol to provide dihydropyridines of general formula (16). Some dicarbonyl compounds of general formula (15) may be prepared as described in (Nakagawa, S., Heterocycles 13 (1979) 477; D'Angelo, J., Tetrahedron Letters 32 (1991) 3063.

Scheme 4



Dihydropyridines of the general formula (17), wherein A, R_1, and n' are as defined in formula I, can be prepared as described in Scheme 4. Dicarbonyl compounds of general formula (15), aldehydes of general formula (7), and cyclic enaminones of general formula (8) can be combined in ethanol and heated to provide dihydropyridines of the general formula (17).

Scheme 5



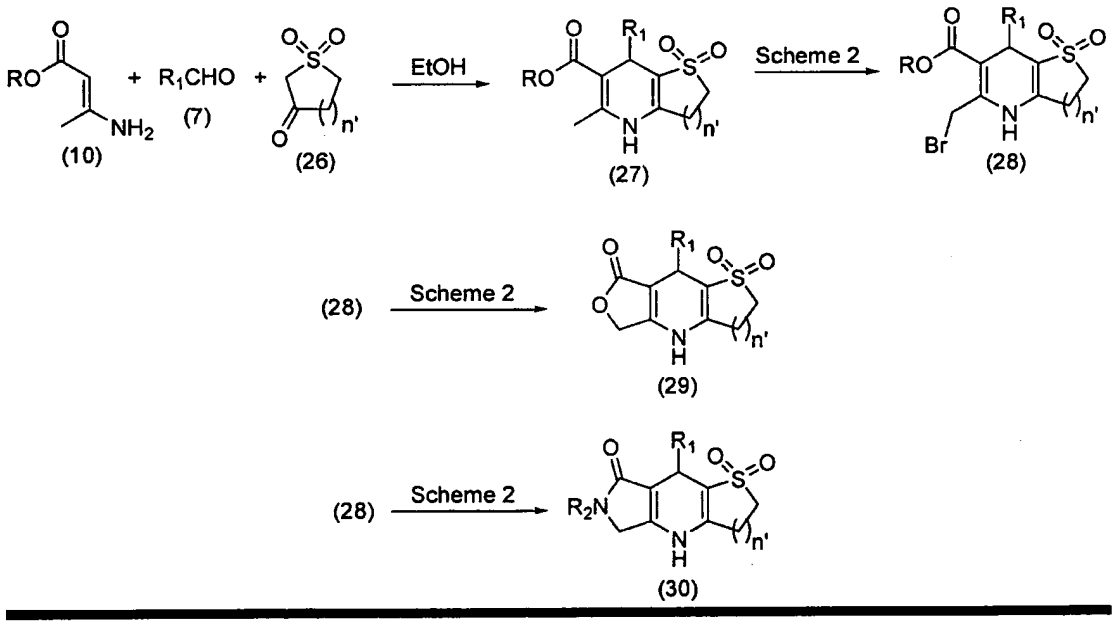
Dihydropyridines of general formula (22-25), wherein R_1, R_2, and n' are as defined in formula I, can be prepared as described in Scheme 5. Dihydropyridines of general formula (9), from Scheme 2, can be treated with boron trichloride in methylene chloride to provide dihydropyridines of general formula (18). Dihydropyridines of general formula (18) can be treated with thionyl chloride and then (+) or (-) mandelic acid to provide diastereomers of general formula (19) and (20). Diastereomers of general formula (19) and (20) can be separated by column chromatography on silica gel. Each separated diastereomeric ester can then be processed as described in Scheme 2 to provide enantiomeric dihydropyridines of general formula (22-25).

Enantiomeric dihydropyridines of general formula (22-25) can be prepared using an alternative method. Diastereomers of general formula (19) and (20) can be treated with MeOH/NaOMe to provide the trans esterified compounds. The methyl esters can then be treated as described in Scheme 2 to provide enantiomeric dihydropyridines of general formula (22-25).

In addition to the use of the method illustrated in Scheme 5, individual enantiomers of compounds of the present Invention may be also be separated by chiral chromatography.

Both of the aforementioned methods of obtaining single enantiomers of the invention may also be applied to the preparation of other compounds, the methods for the preparation of which appear in the Schemes 6-41.

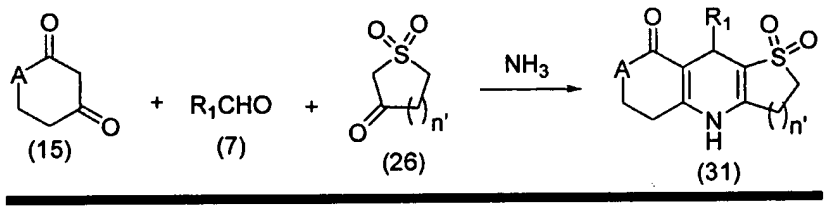
Scheme 6



Dihydropyridines of general formula (29) and (30), wherein R_1, R_2, and n' are as defined in formula I, can be prepared as described in Scheme 6. 3-Aminocrotonates of general formula (10), wherein R is lower alkyl, aldehydes of general formula (7), and cyclic β-keto sulfones of general formula (26) can be combined and heated in a solvent such as ethanol, methanol, acetonitrile or toluene to provide dihydropyridines of general

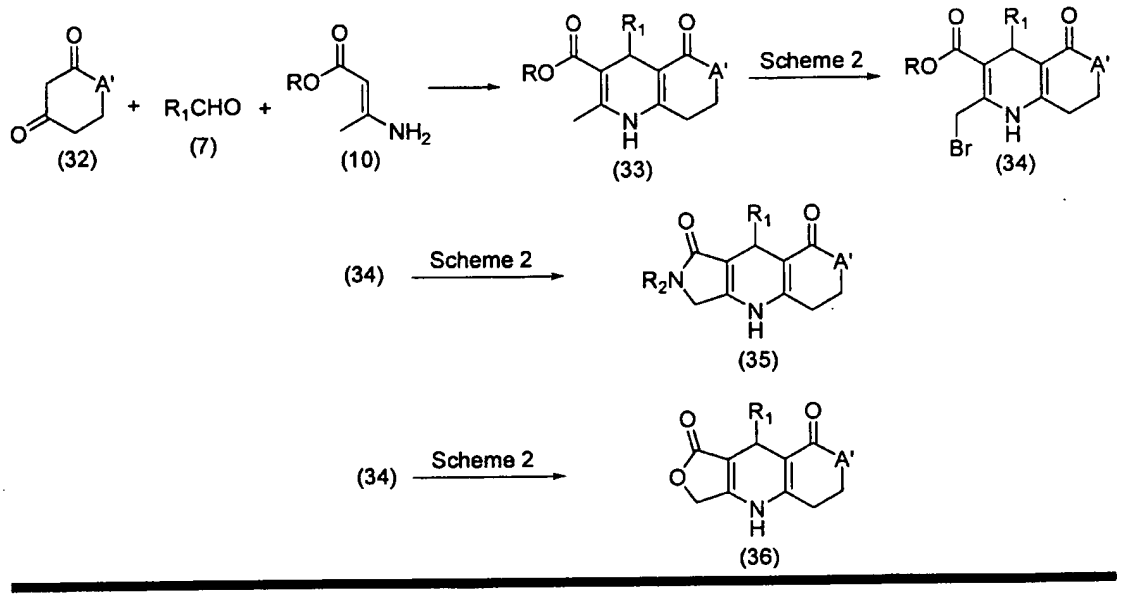
formula (27). In the case where n'=1, an additional heating step at an elevated temperature in the presence or the absence of an acid such as hydrochloric acid or para-toluenesulfonic acid may be necessary to drive the reaction to completion. Dihydropyridines of general formula (27) can be processed as described in Scheme 2, using reagents such as NBS, pyridinium tribromide or a similar brominating agent, to provide dihydropyridines of general formula (28). Dihydropyridines of general formula (28) can be processed as described in Scheme 2 to provide dihydropyridines of general formula (29) and (30). Dihydropyridines of general formula (27) may also be treated with chlorinating reagents such as SO_2Cl_2, PCl_5 or NCS to provide the analgous chloromethyl derivatives which can also be processed as described in Scheme 2 to provide dihydropyridines of general formula (29) and (30).

Scheme 7



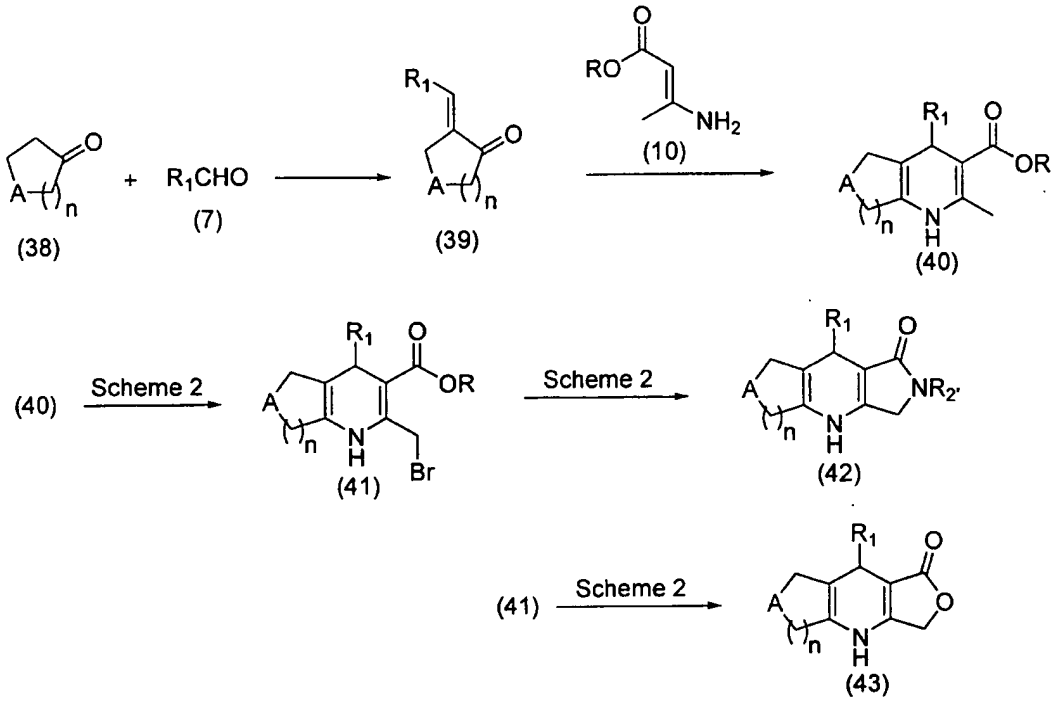
Dihydropyridines of general formula (31), wherein A, R_1, and n' are as defined in formula I, can be prepared as described in Scheme 7. Dicarbonyl compounds of general formula (15) can be treated with a suitable ammonia source such as NH_3, NH_4OH or NH_4OAc, then aldehydes of general formula (7) and cyclic β-keto sulfones of general formula (26) can be added and the reaction mixture heated to provide dihydropyridines of general formula (31). In the case where n'=1, an additional heating step at elevated temperature in the presence or the absence of an acid such as hydrochloric acid or para-toluenesulfonic acid may be necessary to drive the reaction to completion.

Scheme 8



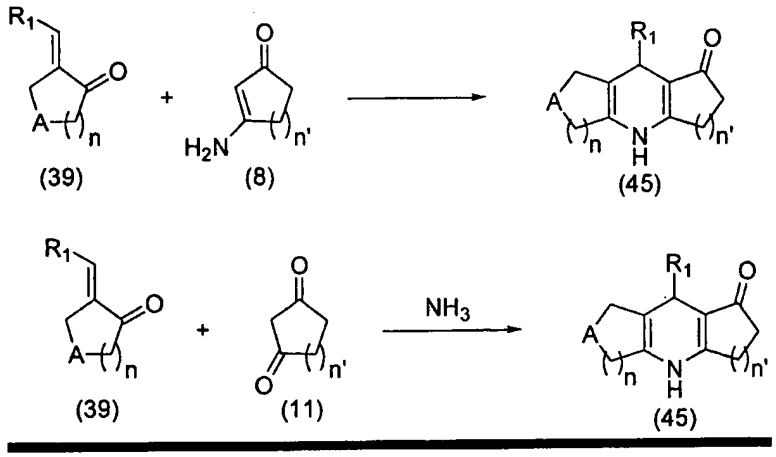
Dihydropyridines of the general formula (35) and (36), wherein R_1, R_2, and A' are as defined in formula I, can be prepared as described in Scheme 8. 3-Aminocrotonates of general formula (10), wherein R is lower alkyl, aldehydes of general formula (7), and cyclic dicarbonyls of general formula (32), preparation of some dicarbonyls is described in (Nakagawa, S., Heterocycles 13 (1979) 477; D'Angelo, J., Tetrahedron Letters 32 (1991) 3063), can be combined and heated in a solvent such as ethanol, methanol, acetonitrile or toluene to provide dihydropyridines of general formula (33). Dihydropyridines of general formula (33) can be processed as described in Scheme 2 with NBS, pyridinium tribromide or similar brominating agents to provide dihydropyridines of general formula (34). Dihydropyridines of general formula (34) can be processed as described in Scheme 2 to provide dihydropyridines of the general formulas (35) and (36). The preparation of compounds of general formula (35) and (36) may also be accomplished via the chloro analog of (34).

Scheme 9



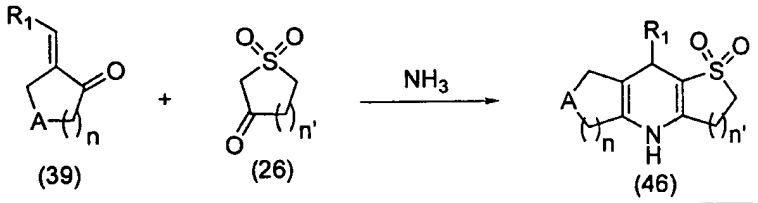
Dihydropyridines of general formulas (42) and (43), wherein R_1, $R_{2'}$, A, and n are as defined in formula I, can be prepared as described in Scheme 9. Condensation of carbonyl compounds of general formula (38) with aldehydes of general formula (7) using the Aldol reaction provides α,β-unsaturated ketones of general formula (39). The reaction is preferably performed by first forming an enamine derivative of (38) with a secondary amine such as morpholine, pyrrolidine, or piperidine. The enamine obtained is then treated directly with (7) under thermal conditions to form (39). α,β-Unsaturated ketones of general formula (39) can be treated with 3-aminocrotonates of general formula (10), wherein R is lower alkyl, such as methyl 3-aminocrotonate, to provide dihydropyridines of general formula (40). An alternate method of preparing (40) can be accomplished with (39), methyl acetoacetate, and ammonia with heating. Dihydropyridines of general formula (40) can be processed as described in Scheme 2 to provide bromomethyl dihydropyridines of general formula (41). Dihydropyridines of general formula (41) can also be processed as desribed in Scheme 2 to provide dihydropyridines of general formula (42) and (43).

Scheme 10



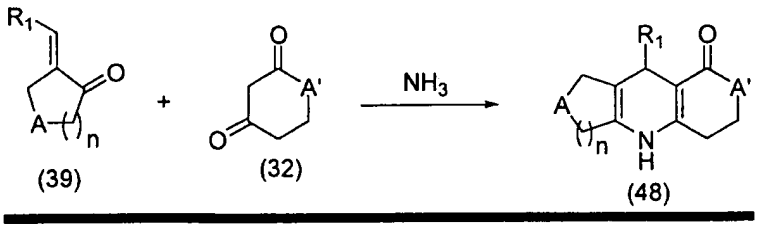
Dihydropyridines of general formula (45), wherein R_1, A, n, and n' are as defined in formula I, can be prepared as described in Scheme 10. α,β-Unsaturated ketones of general formula (39), from Scheme 9, can be treated with cyclic enaminones of general formula (8) with heating to provide dihydropyridines of general formula (45). An alternate method uses (39), ammonia and dicarbonyl compounds of general formula (11), with heat to provide (45).

Scheme 11



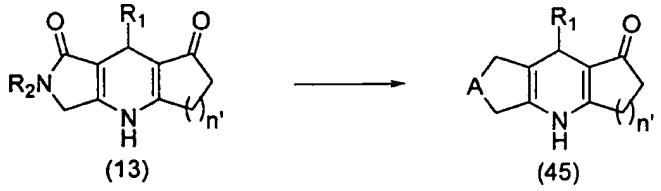
Dihydropyridines of general formula (46), wherein R_1, A, n, and n' are as defined in formula I, can be prepared as described in Scheme 11. α,β-Unsaturated ketones of general formula (39), from Scheme 9, can be treated with cyclic β-keto sulfones of general formula (26) and a suitable source of ammonia (see Scheme 7) with heating to produce dihydropyridines of general formula (46).

Scheme 12



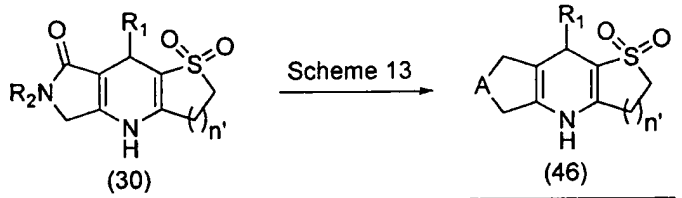
Dihydropyridines of general formula (48), wherein R_1, A, A', and n are as defined in formula I, can be prepared as described in Scheme 12. α,β-Unsaturated ketones of general formula (39), from Scheme 9, can be treated with dicarbonyl compounds of general formula (32) and ammonia or suitable source of ammonia (see Scheme 7) with heating to provide dihydropyridines of general formula(48).

Scheme 13



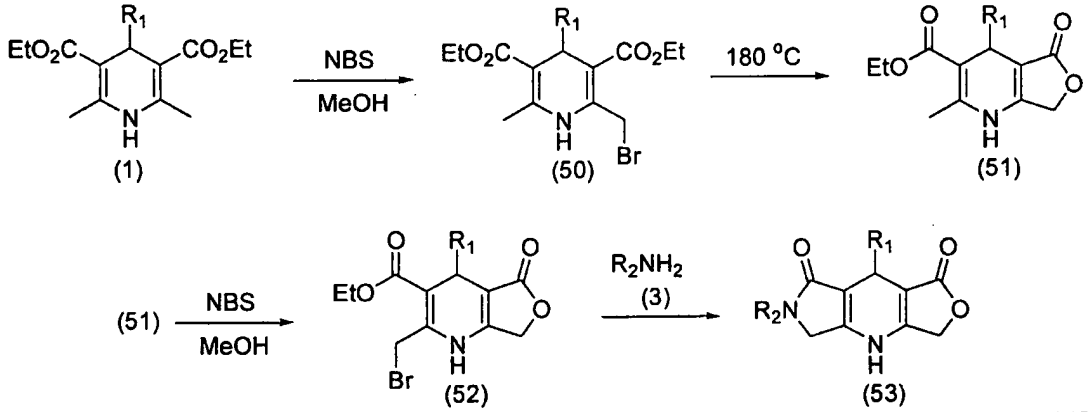
An alternate method of preparing dihydropyridines of general formula (45), wherein A is NR_2 and R_2 and n' are as defined in formula I, can be accomplished as described in Scheme 13. Dihydropyridines of general formula (13), from Scheme 2, can be reduced to provide dihydropyridines of general formula (45). Preferably, this transformation can be accomplished by conversion of (13) to the iminoether with trimethyl or triethyloxonium tetrafluoroborate and reduction with sodium borohydride. Alternatively, the amide can be converted to the thioamide using Lawesson's reagent. Desulfurization of the thioamide can be accomplished with Raney Nickel under a hydrogen atmosphere. Desulfurization can also be accomplished by conversion to the sulfonium species via addition of an alkyl halide such iodomethane and then reduction with sodium borohydride.

Scheme 14



An alternate method of preparing dihydropyridines of general formula (46), wherein A is NR_2 and R_2 and n' are as defined in formula I, can be accomplished as described in Scheme 14. Dihydropyridines of general formula (30), from Scheme 6, can be reduced to provide dihydropyridines of general formula (46) as described in Scheme 13. Preferably, this transformation can be accomplished by conversion of (30) to the iminoether with trimethyl or triethyloxonium tetrafluoroborate and reduction with sodium borohydride.

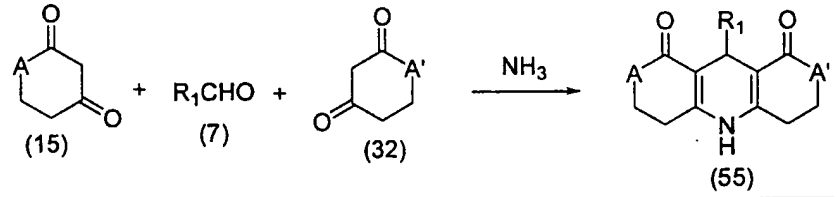
Scheme 15



Dihydropyridines of general formula (53), wherein R_1 and R_2 are as defined in formula I, can be prepared as described in Scheme 15. Dihydropyridine (1), from Scheme 1, can be mono brominated to provide (50) and then heated at 180 °C to provide dihydropyridine (51). Dihydropyridine (51) can be brominated to provide dihydropyridine (52). Dihydropyridine (52) can then be treated with primary amines of general formula (3) as described in Scheme 2 to provide dihydropyridines of general formula (53). Alternatively the sequence of reactions can be rearranged as dihydropyridine (50) can be

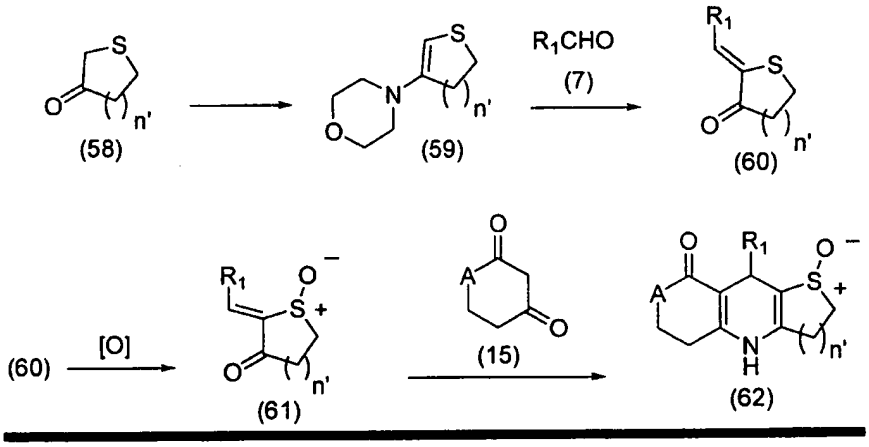
treated with a primary amine of general formula (3) followed by a brominating agent as described in Scheme 2 and then heat to provide dihydropyridines of general formula (53).

Scheme 16



Dihydropyridines of general formula (55), wherein R_1, A, and A' are as defined in formula I, can be prepared as described in Scheme 16. Dicarbonyl compounds of general formula (15) can be treated with ammonia and then treated with aldehydes of general formula (7) and dicarbonyl compounds of general formula (32) with heating to provide dihydropyridines of general formula (55).

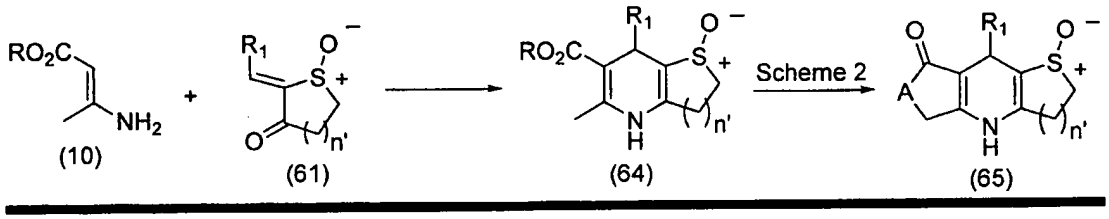
Scheme 17



Dihydropyridines of general formula (62), wherein R_1, A, and n' are as defined in formula I, can be prepared as described in Scheme 17. Carbonyl compounds of general formula (58) can be treated with secondary amines such as morpholine, pyrrolidine or piperidine to provide enamines (59). Enamines (59) can be treated aldehydes of general formula (7) in an appropriate organic solvent to provide sulfides of general formula (60).

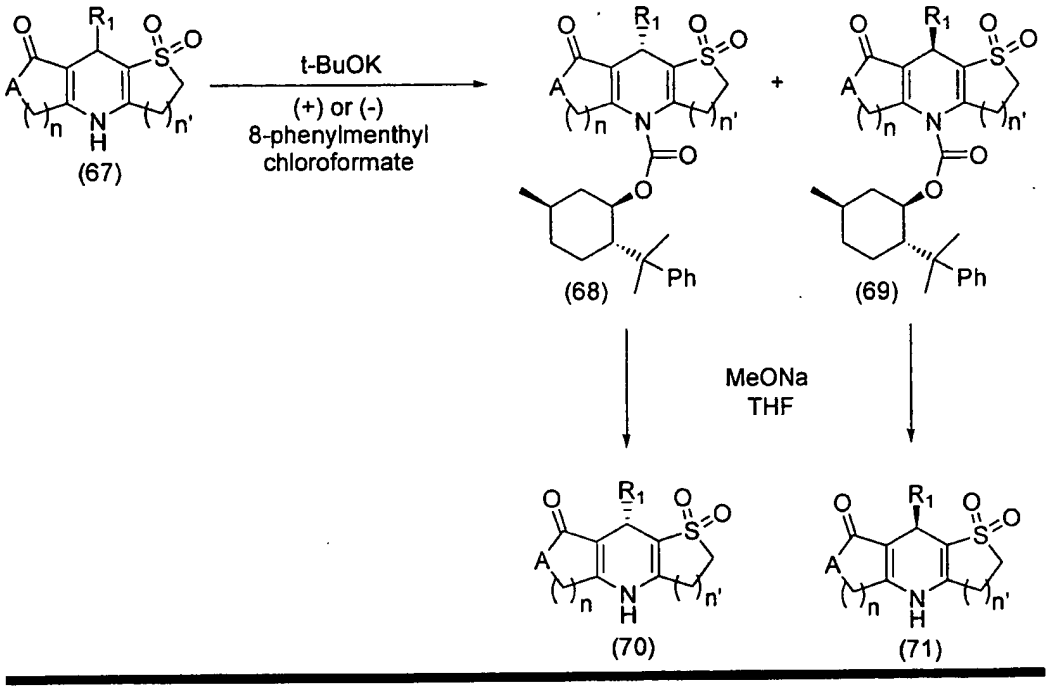
Oxidation of the sulfide with an oxidant such as meta-chloroperoxybenzoic acid provides sulfoxides of general formula (61) that can then be treated with dicarbonyl compounds of general formula (15) and a source of ammonia such as ammonia, ammonium acetate or ammonium hydroxide with heating in a solvent such as ethyl alcohol or similar alcoholic solvent, acetonitrile or dimethylformamide to provide dihydropyridines of general formula (62).

Scheme 18



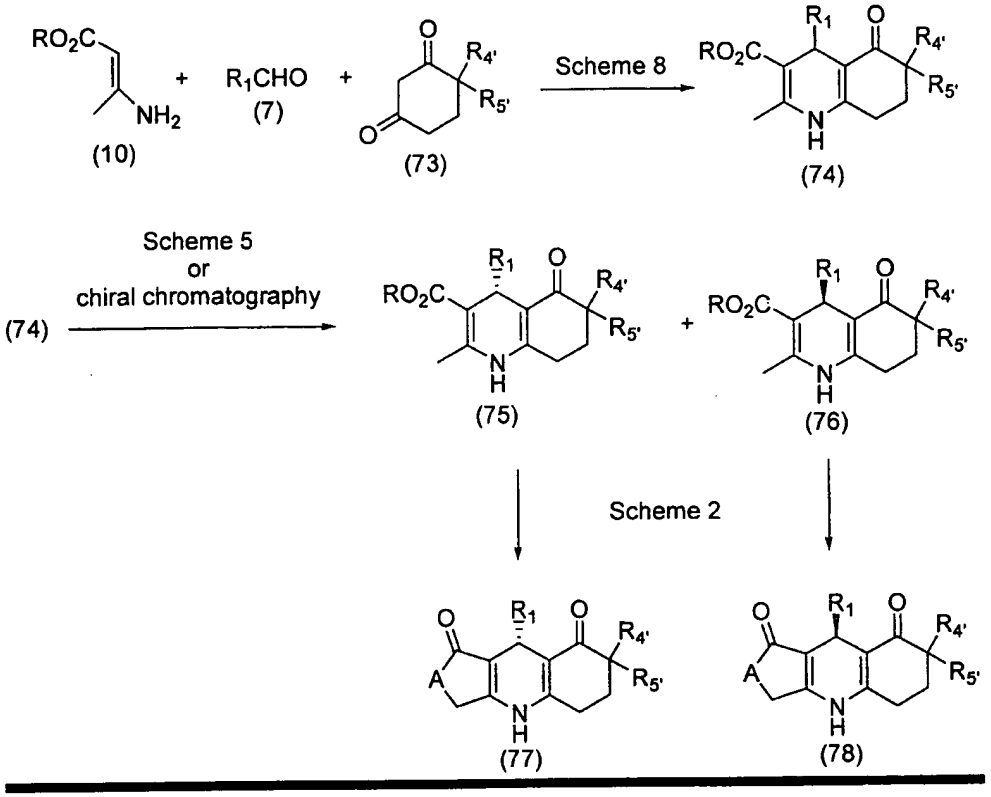
Dihydropyridines of general formula (65), wherein R_1, A, and n' are as defined in formula I, can be prepared as described in Scheme 18. 3-Aminocrotonates of general formula (10) can be treated with sulfoxides of general formula (61), from Scheme 17, with heating in a solvent such as ethyl alcohol or similar alcoholic solvent, acetonitrile or dimethylformamide to provide bicyclic dihydropyridine sulfoxides of general formula (64). Dihydropyridine sulfoxides of general formula (64) can then be processed as described in Scheme 2 to provide dihydropyridines of general formula (65).

Scheme 19



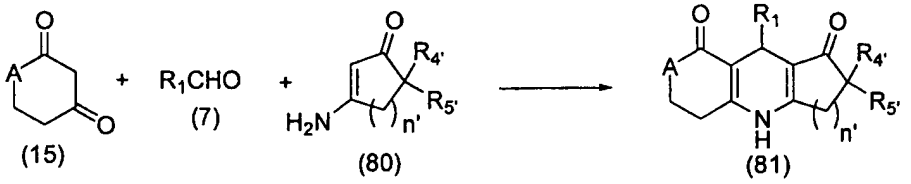
Dihydropyridines of general formula (70) and (71), wherein R_1, A, n, and n' are as defined in formula I, can be prepared as described in Scheme 19. Racemic sulfones of general formula (67) can be treated with potassium t-butoxide (1 equivalent) in tetrahydrofuran followed by (+) or (-) 8-phenylmenthyl chloroformate to generate a mixture of diastereomeric 8-phenylmenthyl carbamates (68) and (69). The diastereomers (68) and (69) can be separated by column chromatography over silica gel and the 8-phenylmenthol moiety removed by reaction with sodium methoxide in methanol to provide single enantiomers of general formula (70) and (71).

Scheme 20



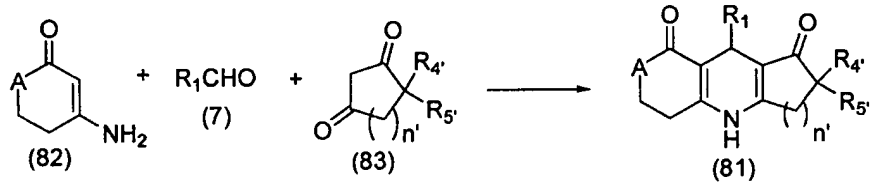
Dihydropyridines of general formula (77) and (78), wherein R_1, $R_{4'}$, $R_{5'}$, and A are as defined in formula I, can be prepared as described in Scheme 20. 3-Aminocrotonates of general formula (10) can be treated with aldehydes of general formula (7) and alkyl substituted cycloalkanediones of general formula (73) as described in Scheme 8 to provide dihydropyridines of general formula (74). Dihydropyridines of general formula (74) can be separated into individual enantiomers (75) and (76) using either chiral chromatography or the method from Scheme 5. Enantiomers (75) and (76) can be processed as described in Scheme 2 to provide enantiomeric dihydropyridines of general formula (77) and (78).

Scheme 21



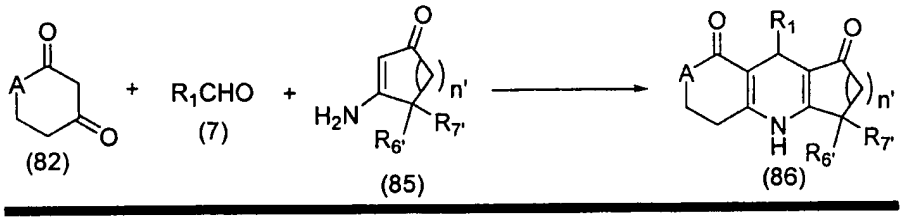
Dihydropyridines of general formula (81), wherein R_1, $R_{4'}$, $R_{5'}$, A and n' are as defined in formula I, can be prepared as described in Scheme 21. Dicarbonyl compounds of general formula (15) can be treated with aldehydes of general formula (7) and alkyl substituted cyclic enaminones of general formula (80) with heating in a solvent such as ethyl alcohol or other similar alcoholic solvent, acetonitrile, or dimethylformamide to provide dihydropyridines of general formula (81).

Scheme 22



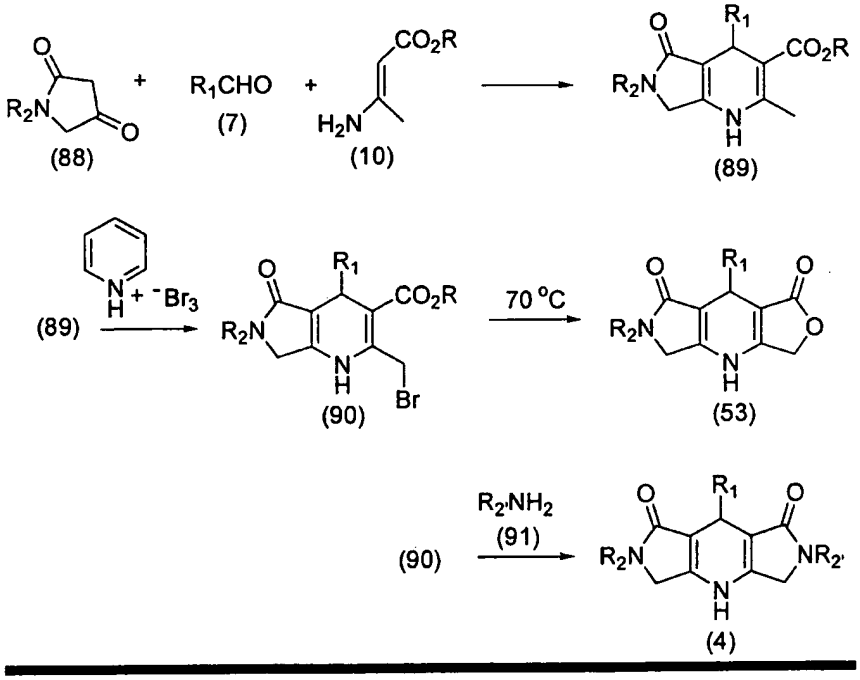
An alternative method of preparing dihydropyridines of general formula (81), wherein R_1, $R_{4'}$, $R_{5'}$, A and n' are as defined in formula I, can be used as described in Scheme 22. Heterocyclic enamines of general formula (82) can be treated with aldehydes of general formula (7) and alkyl substituted cyclic diones of general formula (83) with heating in a solvent such as ethyl alcohol or other similar alcoholic solvent, acetonitrile, or dimethylformamide to provide dihydropyridines of general formula (81).

Scheme 23



Dihydropyridines of general formula (86), wherein R_1, $R_{6'}$, $R_{7'}$, A and n' are as defined in formula I, can be prepared as described in Scheme 23. Heterocyclic dicarbonyl compounds of general formula (82) can be treated with aldehydes of general formula (7) and alkyl substituted cyclic enaminones of general formula (85) with heating in a solvent such as ethyl alcohol or other similar alcoholic solvent, acetonitrile, or dimethylformamide to provide dihydropyridines of general formula (86).

Scheme 24

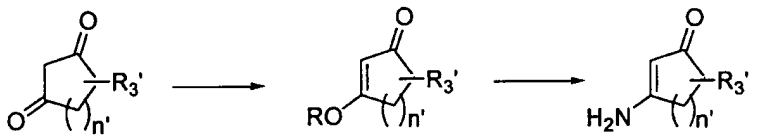


Alternative methods of preparing dihydropyridines of general formula (53) and (4), wherein R_1, R_2, and $R_{2'}$ are as defined in formula I, can be used as described in Scheme 24. 2,4-Pyrrolidinedione derivatives of general formula (88), aldehydes of general formula (7), and 3-aminocrotonates of general formula (10), wherein R is lower alkyl, can be

condensed to provide dihydropyridines of general formula (89). Dihydropyridines of general formula (89) can be treated with a suitable brominating agent such as pyridinium bromide perbromide or N-bromosuccinimide in a solvent such as chloroform or methanol to provide dihydropyridines of general formula (90). Dihydropyridines of general formula (90) can be heated at 70 °C to provide dihydropyridines of general formula (53). Dihydropyridines of general formula (90) can also be heated in the presence of a primary amine of general formula (91) to provide dihydropyridines of general formula (4).

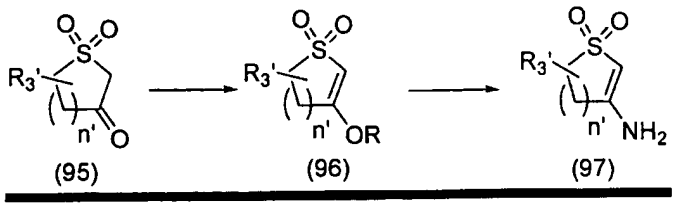
Many of the starting materials necessary to carry out the methods described in the preceeding Schemes may be purchased from commercial sources whereas others are known in the chemical literature. Appropriate literature references may be found in the following section or in the Examples section for such known entities. For starting materials not previously described in the literature the following Schemes are intended to illustrate their preparation through a general method.

Scheme 25



Enamines of general formula (94), wherein n' is an integer 1-3 and R_3, is absent or can be 1 or 2 substituents independently selected from alkyl can be prepared according to the general method shown in Scheme 25. This method entails reaction of an appropriate cycloalkanedione of general formula (92) with an alcohol such as ethanol or methanol with catalysis by an acid such as sulfuric acid or hydrochloric acid or other similar acid to form an intermediate enol ether of general formula (93), wherein R is lower alkyl such as ethyl or methyl. The enol ether (93) can be converted to an enamine of general formula (94) by reaction with ammonia typically in a solvent such as methanol, ethanol or tetrahydrofuran. This method is preferred for the preparation of 3-amino-4,4-dimethyl-2-cyclohexen-1-one and 3-amino-6,6-dimethyl-2-cyclohexen-1-one.

Scheme 26

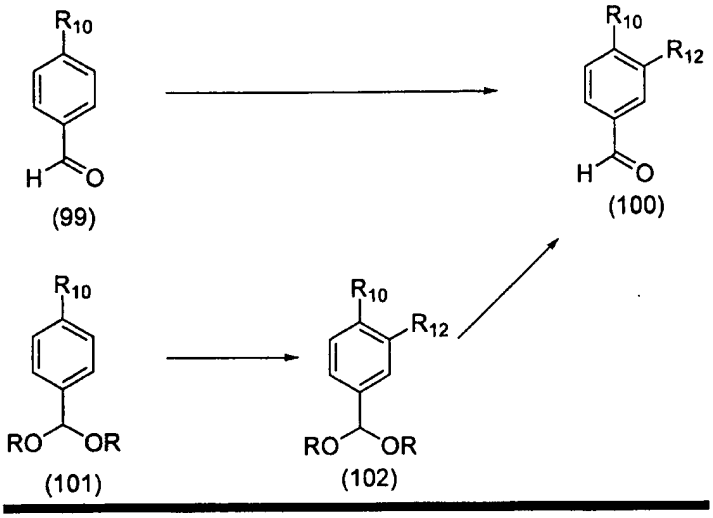


As shown in Scheme 26, enamines of general formula (95), wherein n' is an integer from 1-3 and $R_{3'}$ is absent or can be 1 or 2 substituents independently selected from alkyl can be prepared by procedures directly analogous to those described in Scheme 25 wherein the carbonyl compound of general formula (95) can be converted to an intermediate enol ether of general formula (96), wherein R is lower alkyl, and then to the enamine (97).

Many of the starting aryl and heteroaryl aldehydes necessary to carry out the methods described in the preceeding and following Schemes may be purchased from commercial sources or may be synthesized by known procedures found in the chemical literature. Appropriate literature references for the preparation of aryl and heteroaryl aldehydes may be found in the following section or in the Examples. For starting materials not previously described in the literature the following Schemes are intended to illustrate their preparation through a general method.

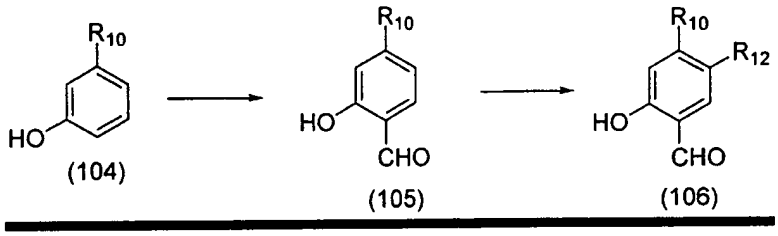
The preparation of aldehydes used to synthesize many preferred compounds of the invention may be found in the following literature references: Pearson, Org. Synth. Coll. Vol V (1973), 117; Nwaukwa, Tetrahedron Lett. (1982), 23, 3131; Badder, J. Indian Chem. Soc. (1976), 53, 1053; Khanna, J. Med. Chem. (1997), 40, 1634; Rinkes, Recl. Trav. Chim. Pays-Bas (1945), 64, 205; van der Lee, Recl. Trav. Chim. Pays-Bas (1926), 45, 687; Widman, Chem. Ber. (1882), 15, 167; Hodgson, J. Chem. Soc. (1927), 2425; Clark, J. Fluorine Chem. (1990), 50, 411; Hodgson, J. Chem. Soc. (1929), 1635; Duff, J. Chem. Soc. (1951), 1512; Crawford, J. Chem. Soc. (1956), 2155; Tanouchi, J. Med. Chem. (1981), 24, 1149; Bergmann, J. Am. Chem. Soc. (1959), 81, 5641; Other: Eistert, Chem. Ber. (1964), 97, 1470; Sekikawa, Bull. Chem. Soc. Jpn. (1959), 32, 551.

Scheme 27



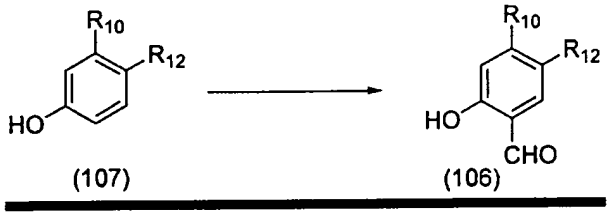
Meta, para-disubstituted aldehydes of general formula (100), wherein R_{10} is selected from alkyl, haloalkyl, halo, haloalkoxy, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl and R_{12} is selected from nitro, halo, and alkylcarbonyl, can be prepared according to the method described in Scheme 27. A para substituted aldehyde of general formula (99) or the corresponding acetal protected aldehyde of general formula (101), wherein R is selected from alkyl or together with the oxygen atoms to which they are attached form a 5 or 6 membered ring wherein 1,3-dioxolanes are preferred, may by subjected to conditions of an electrophilic aromatic substitution reaction to provide aldehydes of general formula (100) or protected aldehydes of general formula (102). Preferred protecting groups for compounds of general formula (101) and (102) include dimethyl or diethyl acetals or the 1,3-dioxolanes. These protecting groups can be introduced at the beginning and removed at the end to provide substituted aldehydes of general formula (100) using methods well known to those skilled in the art of organic chemistry.

Scheme 28



Aldehydes of general formula (106), wherein R_{10} is selected from alkyl, haloalkyl, halo, haloalkoxy, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl and R_{12} is selected from nitro, halo, and alkylcarbonyl, can be prepared by the method described in Scheme 28. A meta substituted phenol (104) is converted to the para substituted salicylaldehyde (105) by reaction with a base such as sodium hydroxide and a reagent such as trichloromethane or tribromomethane, known as the Reimer-Tiemann reaction. An alternate set of reaction conditions involves reaction with magnesium methoxide and paraformaldehyde (Aldred, J. Chem. Soc. Perkin Trans. 1 (1994), 1823). The aldehyde (105) may be subjected to conditions of an electrophilic aromatic substitution reaction to provide meta, para disubstituted salicylaldehydes of general formula (106).

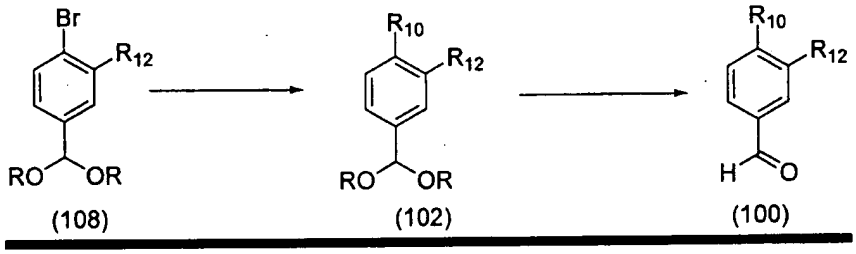
Scheme 29



An alternative method of preparing meta, para disubstituted salicylaldehydes of general formula (106), wherein R_{10} is selected from alkyl, haloalkyl, halo, haloalkoxy, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl and R_{12} is selected from nitro, halo, and alkylcarbonyl, can be used as described in Scheme 29. A meta, para disubstituted phenol of general formula (107) can be reacted with a base such as sodium hydroxide and a reagent such as trichloromethane or tribromomethane, known as the

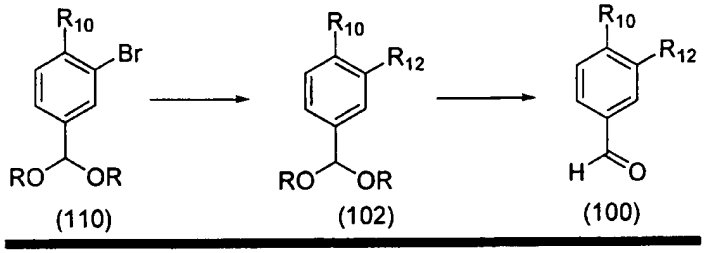
Reimer-Tiemann reaction, to provide disubstituted salicylaldehydes of general formula (106). An alternate set of reaction conditions involves reaction with magnesium methoxide and paraformaldehyde (Aldred, J. Chem. Soc. Perkin Trans. 1 (1994), 1823).

Scheme 30



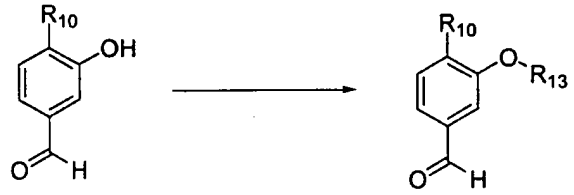
An alternative method of preparing benzaldehydes of general formula (100), wherein R_{12} is selected from alkyl, haloalkyl, chlorine, fluorine, haloalkoxy, alkoxy, alkylthio, nitro, alkylcarbonyl, arylcarbonyl, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{10} is selected from alkyl, hydroxyalkyl, alkylthio, alkylcarbonyl, and formyl, is described in Scheme 30. Protected benzaldehydes of general formula (108), wherein R is selected from alkyl or together with the oxygen atoms to which they are attached form a 5 or 6 membered ring wherein 1,3-dioxolanes are preferred, can be converted to the 3,4-disubstituted benzaldehyde of general formula (102) via conversion of the bromide to an intermediate lithio or magnesio derivative, followed by reaction with an appropriate electrophile such as an aldehyde, dialkyldisulfide, a Weinreb amide, dimethylformamide, an alkyl halide or other electrophile followed by deprotection of the acetal to provide benzaldehydes of general formula (100).

Scheme 31



An alternative method of preparing benzaldehydes of general formula (100), wherein R_{10} is selected from alkyl, haloalkyl, chlorine, fluorine, haloalkoxy, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, R_{12} is selected from alkyl, hydroxyalkyl, alkylthio, alkylcarbonyl, arylcarbonyl, and formyl, can be used as described in Scheme 31. Protected benzaldehydes of general formula (110), wherein R is selected from alkyl or together with the oxygen atoms to which they are attached form a 5 or 6 membered ring wherein 1,3-dioxolanes are preferred can be processed as described in Scheme 30 to provide benzaldehydes of general formula (100).

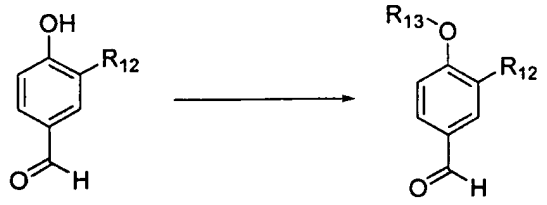
Scheme 32



Benzaldehydes of general formula (113), wherein R_{10} is selected from hydrogen, alkyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, halo, haloalkoxy, nitro, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{13} is selected from hydrogen, alkyl, arylalkyl, and haloalkyl wherein preferred haloalkyl groups are selected from difluoromethyl, 2,2,2-trifluoroethyl and bromodifluoromethyl, can be prepared as described in Scheme 32. 3-Hydroxybenzaldehyde of general formula (112) can be treated with suitable alkylating reagents such as benzylbromide, iodomethane, 2-iodo-1,1,1-

trifluoroethane, chlorodifluoromethane, or dibromodifluoromethane in the presence of base such as potassium carbonate, potassium tert-butoxide or sodium tert-butoxide, to provide benzaldehydes of general formula (113). The synthesis of useful 3-hydroxybenzaldehydes of general formula (112) may be found in the following literature references: J. Chem. Soc. (1923), 2820; J. Med Chem. (1986), 29, 1982; Monatsh. Chem. (1963), 94, 1262; Justus Liebigs Ann. Chem. (1897), 294, 381; J. Chem. Soc. Perkin Trans. 1 (1990), 315; Tetrahedron Lett. (1990), 5495; J. Chem. Soc. Perkin Trans. 1 (1981), 2677.

Scheme 33

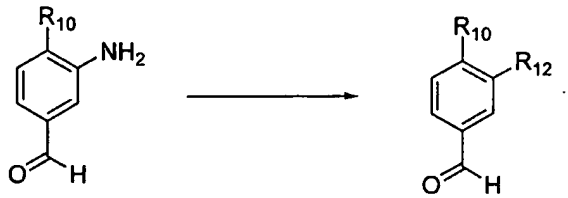


(114) (115)

Benzaldehydes of general formula (115), wherein R_{12} is selected from hydrogen, alkyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, halo, haloalkoxy, nitro, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{13} is selected from hydrogen, alkyl, arylalkyl, and haloalkyl wherein preferred haloalkyl groups are selected from difluoromethyl, 2,2,2-trifluoroethyl, and bromodifluoromethyl, can be prepared as described in Scheme 33. 4-Hydroxybenzaldehydes of general formula (114) can be treated with suitable alkylating reagents such as benzylbromide, iodomethane, 2-iodo-1,1,1-trifluoroethane, chlorodifluoromethane, or dibromodifluoromethane, in the presence of base such as potassium carbonate, potassium tert-butoxide or sodium tert-butoxide to provide benzaldehydes of general formula (115). The synthesis of useful 4-hydroxybenzaldehydes of general formula (114) may be found in the following literature references: Angyal, J. Chem. Soc. (1950), 2141; Ginsburg, J. Am. Chem. Soc. (1951), 73, 702; Claisen, Justus Liebigs Ann. Chem. (1913), 401, 107; Nagao, Tetrahedron Lett. (1980), 21, 4931; Ferguson, J. Am. Chem. Soc. (1950), 72, 4324; Barnes, J. Chem. Soc.

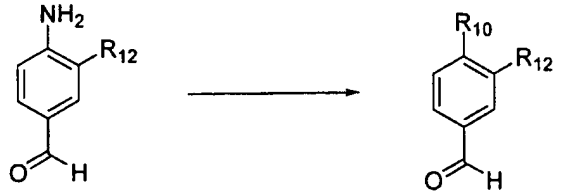
(1950), 2824; Villagomez-Ibarra, Tetrahedron (1995), 51, 9285; Komiyama, J. Am. Chem. Soc. (1983), 105, 2018; DE 87255; Hodgson, J. Chem. Soc. (1929), 469; Hodgson, J. Chem. Soc. (1929), 1641.

Scheme 34



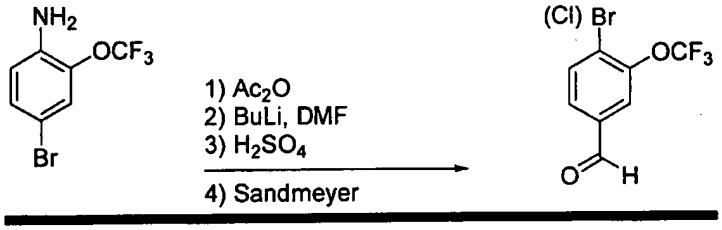
An alternate method for introduction of substituents at the 3-position of benzaldehydes of general formula (100), wherein R_{10} is selected from hydrogen, alkyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, halo, haloalkoxy, nitro, alkoxy, alkylthio, and -C(O)NZ_1Z_2, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl can be used as described in Scheme 34. This method, also known as the Sandmeyer reaction, involves converting 3-amino benzaldehydes of general formula (116) to an intermediate diazonium salt with sodium nitrite. The diazonium salts can be treated with a bromine or iodine source to provide the bromide or iodide. The Sandmeyer reaction and conditions for effecting the transformation are well known to those skilled in the art of organic chemistry. The types of R_{12} substituents that may be introduced in this fashion include cyano, hydroxy, or halo. In order to successfully carry out this transformation it may in certain circumstances be advantageous to perform the Sandmeyer reaction on a protected aldehyde. The resulting iodide or bromide can be treated with unsaturated halides, boronic acids or tin reagents in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) to provide benzaldehydes of general formula (100). The diazonium salts may also be treated directly with unsaturated halides, boronic acids or tin reagents in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) to provide benzaldehydes of general formula (100).

Scheme 35



An alternate method for introduction of substituents at the 4-position of benzaldehydes of general formula (100), wherein R_{12} is selected from hydrogen, alkyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, halo, haloalkoxy, nitro, alkoxy, alkylthio, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, can be used as described in Scheme 35. This method, also known as the Sandmeyer reaction, involves converting 4-amino benzaldehydes of general formula (117) to an intermediate diazonium salt with sodium nitrite and then treating the diazonium salts in a similar manner as that described in Scheme 34. The types of R_{10} substituents that may be introduced in this fashion include cyano, hydroxy, or halo. The Sandmeyer reaction and conditions for effecting the transformation are well known to those skilled in the art of organic chemistry. In order to successfully carry out this transformation it may in certain circumstances be advantageous to perform the Sandmeyer reaction on a protected aldehyde.

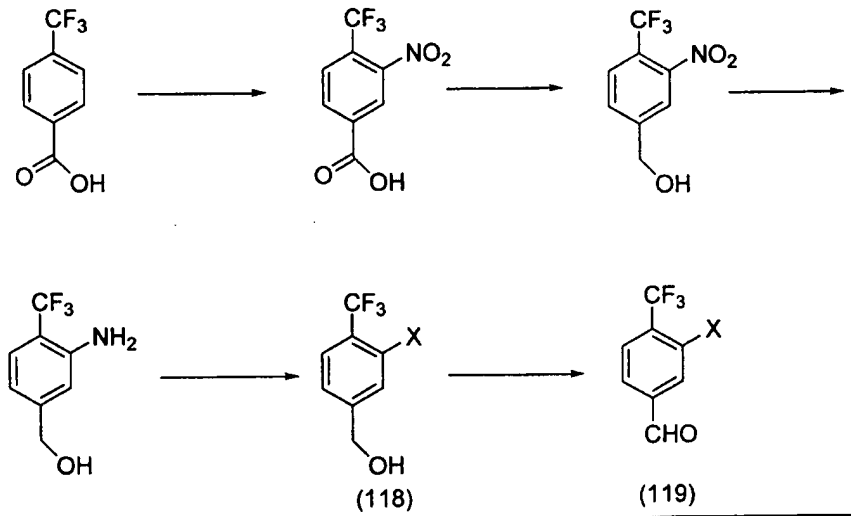
Scheme 36



4-Bromo-3-(trifluoromethoxy)benzaldehyde or 4-chloro-3-(trifluoromethoxy)benzaldehyde can be prepared as described in Scheme 36. The commercially available 4-bromo-2-(trifluoromethoxy)aniline can be protected on the amino group with a suitable N-protecting group well known to those skilled in the art of

organic chemistry such as acetyl or tert-butoxycarbonyl. The bromine can then be converted to the lithio or magnesio derivative and reacted directly with dimethylformamide to provide the 4-aminoprotected-3-(trifluoromethoxy)benzaldehyde derivative. Removal of the N-protecting group followed by conversion of the amine to a bromide or chloride via the Sandmeyer method of Scheme 35 provides 4-bromo-3-(trifluoromethoxy)benzaldehyde or 4-chloro-3-(trifluoromethoxy)benzaldehyde.

Scheme 37

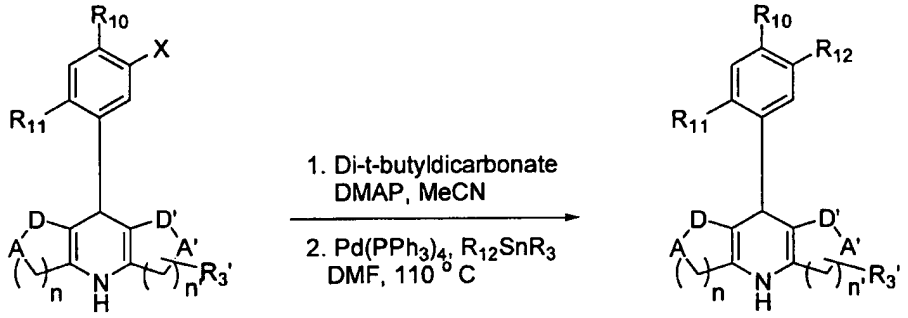


4-Trifluoromethylbenzaldehydes of general formula (119), wherein X is selected from cyano, nitro, and halo may be prepared according to the method of Scheme 37. 4-Trifluoromethylbenzoic acid is first nitrated, using suitable conditions well known in the literature such as nitric acid with sulfuric acid, and the carboxylic acid group reduced with borane to provide 3-nitro-4-trifluoromethylbenzyl alcohol. From this benzyl alcohol may be obtained the 3-nitro-4-trifluoromethylbenzaldehyde by oxidation with typical reagents such as manganese dioxide. The nitro benzylic alcohol can be reduced to the aniline using any of a number of different conditions for effecting this transformation among which a preferred method is hydrogenation over a palladium catalyst. The aniline can be converted to either a halo or cyano substituent using the Sandmeyer reaction described in Scheme 34. Benzyl alcohols of general formula (118) can be oxidized using conditions well known to

those skilled in the art such as manganese dioxide or swern conditions to provide benzaldehydes of general formula (119).

For certain aromatic ring substitutions of R_1 for compounds of the present invention it is preferable to effect transformations of the aromatic ring substitutions after the aldehyde has been incorporated into the core structure of the present invention. As such, compounds of the present invention may be further transformed to other distinct compounds of the present invention. These transformations involve Stille, Suzuki and Heck coupling reactions all of which are well known to those skilled in the art of organic chemistry. Shown below are some representative methods of such transformations of compounds of the present invention to other compounds of the present invention.

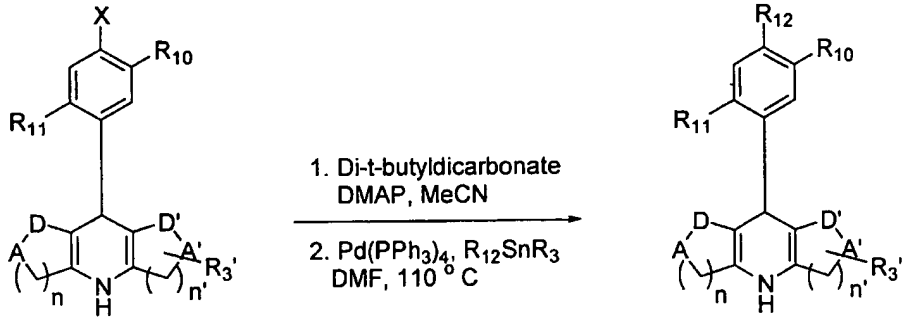
Scheme 38



Dihydropyridines of general formula (121), wherein A, A', D, D', n and n' are as defined in formula I, R_3, is 1 or 2 substituents independently selected from hydrogen or alkyl, R_{10} is selected from hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, and alkylthio, and -$C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, R_{11} is selected from hydrogen, hydroxy, alkoxy, haloalkoxy, and arylalkoxy, R_{12} is selected from alkyl, vinyl, aryl, heteroaryl, cyano and the like, can be prepared as described in Scheme 38. Compounds of general formula (120), wherein X is selected from bromine, iodine, and triflate, are protected with a tert-butoxycarbonyl (Boc) group using standard procedures. The aromatic bromide, iodide, or triflate can be treated with a suitable tin, boronic acid, or unsaturated halide reagent in the

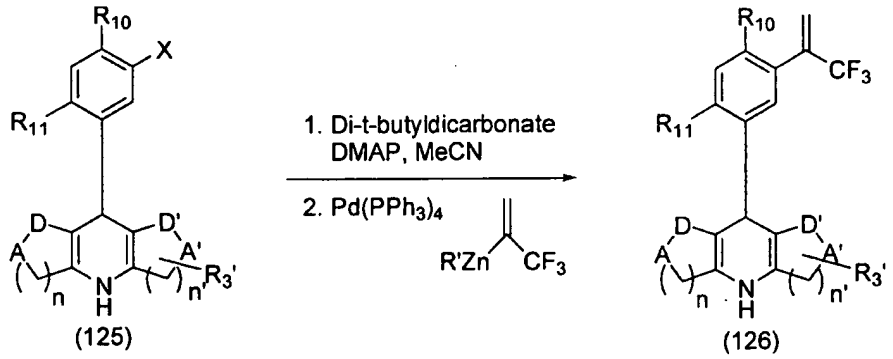
presence of a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides dihydropyridines of general formula (121). The conditions for this transformation also effect the removal of the Boc protecting group.

Scheme 39



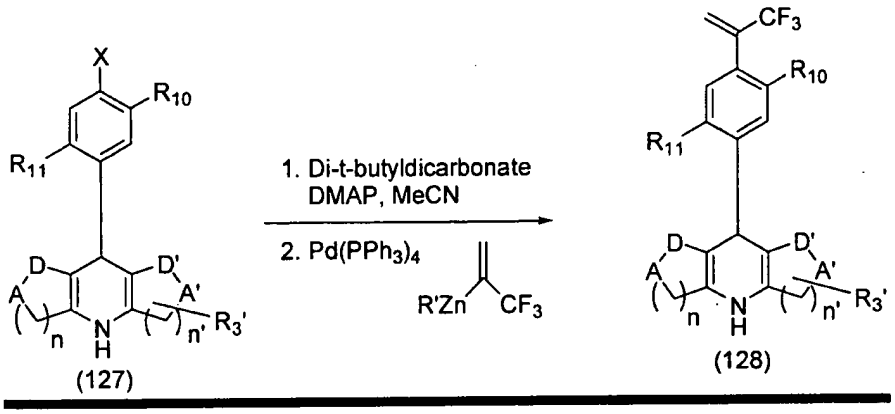
Dihydropyridines of general formula (123), wherein A, A', D, D', n and n' are as defined in formula I, $R_{3'}$ is 1 or 2 substituents independently selected from hydrogen or alkyl, R_{12} is selected from hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, alkylthio, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, R_{11} is selected from hydrogen, hydroxy, alkoxy, haloalkoxy, and arylalkoxy, R_{10} is selected from alkyl, vinyl, aryl, heteroaryl, cyano and the like, can be prepared as described in Scheme 39. Dihydropyridines of general formula (122), wherein X is selected from bromine, iodine, and triflate, can be protected with a tert-butoxycarbonyl (Boc) group using standard procedures. The aromatic bromide, iodide, or triflate can be reacted with a suitable tin, boronic acid, or unsaturated halide reagent in the presence of a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides dihydropyridines of general formula (123). The conditions for this transformation also effect the removal of the Boc protecting group.

Scheme 40



Dihydropyridines of general formula (126), wherein A, A', D, D', n and n' are as defined in formula I, R_3, is 1 or 2 substituents independently selected from hydrogen or alkyl, R_{10} is selected from hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, alkylthio, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{11} is selected from hydrogen, hydroxy, alkoxy, haloalkoxy, and arylalkoxy, can be prepared as described in Scheme 40. Dihydropyridines of general formula (125), wherein X is selected from bromine, iodine, and triflate can be protected with a tert-butoxycarbonyl (Boc) group using standard procedures. The aromatic bromide, iodide, or triflate can be treated with a suitable halozinc reagent in the presence of a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides dihydropyridines of general formula (126). The conditions for this transformation also effect the removal of the Boc protecting group. The types of meta substituents that may be introduced in this fashion include trihalopropenyl and more specifically the trifluoropropenyl group.

Scheme 41



Dihydropyridines of general formula (128), wherein A, A', D, D', n and n' are as defined in formula I, R_3, is 1 or 2 substituents independently selected from hydrogen or alkyl, R_{10} is selected from hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, alkylthio, $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, R_{11} is selected from hydrogen, hydroxy, alkoxy, haloalkoxy, and arylalkoxy, can be prepared as described in Scheme 41. Dihydropyridines of general formula (127), wherein X is selected from bromine, iodine, and triflate can be protected with a tert-butoxycarbonyl (Boc) group using standard procedures. The aromatic bromide, iodide, or triflate can be treated with a suitable halozinc reagent in the presence of a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides dihydropyridines of general formula (128). The conditions for this transformation also effect the removal of the Boc protecting group. The types of para substituents that may be introduced in this fashion include trihalopropenyl and more specifically the trifluoropropenyl group.

The following methods are intended as an illustration of and not a limitation upon the scope of the invention as defined in the appended claims. Further, all citations herein are incorporated by reference.

Example 1

8-(3-bromo-4-fluorophenyl)-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione

Example 1A

diethyl 4-(3-bromo-4-fluorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate

A solution of 3-bromo-4-fluorobenzaldehyde (6.00 g, 29.6 mmol) and ethyl acetoacetate (7.81 g, 60 mmol) in ethyl alcohol (15 mL) and methylene chloride (15 mL) was treated with concentrated ammonium hydroxide (6.2 mL) in two portions over a period of two days with heating at reflux. The reaction was allowed to cool to ambient temperature. The solvent was evaporated and the crude material purified by flash chromatography (1:3-ethyl acetate:hexane) to provide 11.3 g of the title compound as a light yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 6H), 2.35 (s, 6H), 4.10 (m, 4H), 4.94 (s, 1H), 5.56 (s, 1H), 6.95 (t, 1H), 7.18 (m, 1H), 7.42 (dd, 1H);

MS (DCI/NH3) m/z 443 $(M+NH_4)^+$.

Example 1B

diethyl 2,6-bis-(bromomethyl)-4-(3-bromo-4-fluorophenyl)-1,4-dihydro-3,5-pyridine dicarboxylate

A solution of the product from Example 1A (1.27 g, 3.00 mmol) in methyl alcohol (60 mL) was treated with N-bromosuccinimide (1.068 g, 6.00 mmol) and stirred for 1.5 hours at ambient temperature. The reaction was poured into water and the resultant precipitate collected. The precipitate was crystallized from acetone/hexane to provid 685 mg of the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 6H), 4.15 (m, 4H), 4.76 (AB qu, 4H), 4.96 (s, 1H), 6.48 (s, 1H), 6.99 (t, 1H), 7.18 (m, 1H), 7.43 (dd, 1H);

MS (APCI+) m/z 584 $(M+H)^+$.

Example 1C

8-(3-bromo-4-fluorophenyl)-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione

The product from Example 1B (0.29 g, 0.50 mmol) was treated with liquid ammonia (25 mL) in ethyl alcohol (25 mL) in a high pressure bomb for 2 days at ambient

temperature. The solvent was evaporated and the resultant solid triturated with hot ethyl alcohol/ethyl acetate. This solid was washed with water then diethyl ether and dried to provide 26 mg of the title compound as a yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 3.95 (q, 4H), 4.58 (s, 1H), 7.25 (d, 2H), 7.42 (s, 2H), 7.46 (s, 1H), 9.83 (s, 1H);

MS (APCI+) m/z 364 $(M+H)^+$;

MS (APCI-) m/z 362 $(M-H)^-$;

Anal. calcd for $C_{15}H_{11}BrFN_3O_2 \cdot 0.3\ H_2O \cdot 0.5\ C_2H_6O$: C, 48.95; H, 3.75; N, 10.70. Found: C, 48.64; H, 3.96; N, 10.33.

Example 2

8-(3-bromo-4-fluorophenyl)-2,6-dimethyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione

The product from Example 1B (0.812 g, 1.4 mmol) was treated with 2.0 M methyl amine/methyl alcohol (7.0 mL) for 3 hours. The reaction mixture was concentrated and the resultant white precipitate triturated with diethyl ether/methylene chloride/methyl alcohol. The solid was washed with water and dried to give 183 mg of the title compound.

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (s, 6H), 4.05 (q, 4H), 4.59 (s, 1H), 7.22 (d, 2H), 7.45 (d, 1H), 9.88 (s, 1H);

MS (APCI+) m/z 392 $(M+H)^+$;

MS (APCI-) m/z 390 $(M-H)^-$;

Anal. calcd for $C_{17}H_{15}BrFN_3O_2 \cdot 0.25\ H_2O$: C, 51.47; H, 3.94; N, 10.59. Found: C, 51.13; H, 4.19; N, 10.36.

Example 3

8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione

Example 3A

methyl 4-(3-bromo-4-fluorophenyl)-4,5,6,7-tetrahydro-2-methyl-5-oxo-1H-cyclopenta[b]pyridine-3-carboxylate

3-Bromo-4-fluorobenzaldehyde (3.045 g, 15 mmol), methyl acetoacetate (2.09 g, 18 mmol) and 3-aminocyclopent-2-enone (1.45 g, 15 mmol) were heated to 65°C in methyl alcohol for 5 days. The reaction was allowed to cool to ambient temperature and the white precipitate collected, washed with methyl alcohol and dried to provide 2.29 g of the title compound. Flash chromatography (5% methyl alcohol/methylene chloride) of the filtrate provided an additional 1.46 g of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.60 (s, 3H), 4.90 (s, 1H), 6.33 (s, 1H), 6.98 (t, 1H), 7.23 (m, 1H), 7.37 (d, 1H);

MS (APCI+) m/z 380 $(M+H)^+$;

Anal. calcd for $C_{17}H_{15}BrFNO_3$: C, 53.70; H, 3.98; N, 3.68. Found: C, 53.57; H, 3.91; N, 3.48.

Example 3B

methyl 4-(3-bromo-4-fluorophenyl)-2-(bromomethyl)-4,5,6,7-tetrahydro-5-oxo-1H-cyclopenta[b]pyridine-3-carboxylate

A solution of the product from Example 3A (1.9 g, 5.0 mmol) in isopropyl alcohol (30 mL) was treated with N-bromosuccinimide (890 mg, 5.0 mmol) and stirred at ambient temperature for 45 minutes. The solvent was evaporated and the crude flash chromatographed to provide 1.19 g of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (m, 2H), 2.65 (m, 2H), 3.63 (s, 3H), 4.83 (AB q, 2H), 4.90 (s, 1H), 6.80 (br s, 1H), 7.00 (t, 1H), 7.23 (m, 1H), 7.40 (dd, 1H).

Example 3C

8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione

The product from Example 3B (0.110 g, 0.24 mmol) in methyl alcohol (1.5 mL) was treated with 2M methylamine/methyl alcohol (1 mL) and stirred overnight at ambient

temperature. The reaction mixture was concentrated and the crude flash chromatographed (10% methyl alcohol/methylene chloride). The product was triturated with diethyl ether to provide 51.6 mg of the title compound as a white powder.

^{1}H NMR (DMSO-d_6) δ 2.30 (d, 2H), 2.65 (m, 2H), 4.08 (q, 2H), 4.55 (s, 1H), 7.22 (m, 2H), 7.45 (d, 1H), 10.32 (s, 1H);

MS (APCI+) m/z 377 $(M+H)^+$;

MS (APCI-) m/z 375 $(M-H)^-$;

Anal. calcd for $C_{17}H_{14}BrFN_2O_2$: C, 54.13; H, 3.74; N, 7.43. Found: C, 53.76; H, 3.94; N, 7.34.

Example 4

8-(3-bromo-4-fluorophenyl)-2-ethyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione

The product from Example 3B (0.30 g, 0.52 mmol) in methyl alcohol (2 mL) was treated with 2M ethylamine/methyl alcohol (2.5 mL) and stirred 1 hour at ambient temperature. The reaction mixture was concentrated and the crude flash chromatographed (7.5% methyl alcohol/methylene chloride) to provide 100 mg of the title compound as a brown solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (t, 3H), 2.30 (t, 2H), 2.62 (t, 2H), 3.26 (q, 2H), 4.08 (q, 2H), 4.53 (s, 1H), 7.22 (m, 2H), 7.43 (d, 1H), 10.35 (s, 1H);

MS (APCI+) m/z 391 $(M+H)^+$;

MS (APCI-) m/z 389 $(M-H)^-$;

Anal. calcd for $C_{18}H_{16}BrFN_2O_2$: C, 55.26; H, 4.12; N, 7.16. Found: C, 54.92; H, 4.16; N, 6.99.

Example 5

8-(3-bromo-4-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione The product from Example 1B (90 mg) was heated in an oil bath at 180 °C for 1 hour and then allowed to cool to ambient temperature. The residue was triturated with

acetone and the solid collected, washed with acetone, and dried to provide 32 mg of the title compound as a light-yellow solid.

mp >260 °C;

^{1}H NMR (300 MHz, DMSO-d_6) δ 4.69 (s, 1H), 4.98 (q, 4H), 7.32 (m, 2H), 7.57 (d, 1H), 10.73 (s, 1H);

MS (ESI-) m/z 364 $(M-H)^-$;

Anal. Calcd for $C_{15}H_9BrFNO_4$: C, 49.21; H, 2.48; N, 3.83. Found: C, 49.23; H, 2.61; N, 3.69.

Example 6

8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione

The product from Example 3B (85 mg, 0.19 mmol) was heated in an oil bath at 180 °C for 1 hour and then allowed to cool to ambient temperature. The residue was triturated with acetone and the solid collected, washed with acetone, and dried to provide 30 mg of the title compound as an orange solid.

mp >260 °C;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (t, 2H), 2.70 (m, 2H), 4.60 (s, 1H), 4.98 (q, 2H), 7.26 (m, 2H), 7.50 (d, 1H), 10.71 (s, 1H);

MS (ESI-) m/z 362 $(M-H)^-$;

Anal. Calcd for $C_{16}H_{11}BrFNO_3 \cdot 0.2\ H_2O$: C, 51.91; H, 2.97; N, 3.77. Found: C, 52.25; H, 3.12; N, 3.81.

Example 7

8-(3-bromo-4-fluorophenyl)-2-(2-methoxyethyl)-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione

The product from Example 3B (300 mg, 0.65 mmol) in methanol was treated with 2-methoxyethylamine (488 mg, 6.5 mmol) at ambient temperature overnight. The solvent was evaporated and the residue flash chromatographed on silica gel (10%

methanol/methylene chloride). The product was triturated with ether, collected, and dried to provide 93 mg of the title compound as a yellow solid.

mp 100 °C (dec);

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (t, 2H), 2.67 (m, 2H), 3.24 (s, 3H), 3.42 (m, 4H), 4.13 (q, 2H), 4.57 (s, 1H), 7.22 (m, 2H), 7.44 (d, 1H), 10.63 (s, 1H);

MS (ESI+) m/z 421 $(M+H)^+$;

MS (ESI-) m/z 419 $(M-H)^-$;

Anal. Calcd for $C_{19}H_{18}BrFN_2O_3 \cdot 0.2\ H_2O$: C, 53.71; H, 4.37; N, 6.59. Found: C, 53.29; H, 4.59; N, 6.27.

Example 8

9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

Example 8A

methyl 4-(3-Bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate

3-Bromo-4-fluorobenzaldehyde (3.05 g, 15 mmol), methyl 3-aminocrotonate (1.73 g, 15 mmol) and 1,3-cyclohexanedione (1.68 g, 15 mmol) were heated in methanol at reflux for 2 hours and then allowed to cool to ambient temperature. The precipitate was collected and dried to provide 4.89 g of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8-2.1 (m, 2H), 2.25-2.50 (m, 4H), 2.42 (s, 3H), 3.62 (s, 3H), 5.07 (s, 1H), 5.86 (br s, 1H), 6.95 (t, 1H), 7.23 (m, 1H), 7.39 (dd, 1H);

MS (ESI+) m/z 394 $(M+H)^+$.

Example 8B

methyl 4-(3-Bromo-4-fluorophenyl)-2-(bromomethyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate

The product fom Example 8A (3.94 g, 10 mmol) in chloroform (25 mL) and pyridine (0.97 mL, 12 mmol) was treated with 90% pyridinium tribromide (4.26 g, 12

mmol) at -10 °C. The reaction mixture was stirred for 3.5 hours, quenched onto water, and extracted with chloroform (3x). The organic phases were dried ($MgSO_4$), filtered and the solvent evaporated to provide 5.5 g of the title compound as a yellow foam.

^1H NMR (300 MHz, $CDCl_3$) δ 1.80-2.15 (m, 2H), 2.30-2.62 (m, 4H), 3.66 (s, 3H), 4.80 (s, 2H), 5.08 (s, 1H), 6.32 (br s, 1H), 6.97 (t, 1H), 7.23 (m, 1H), 7.42 (dd, 1H).

Example 8C

9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The product from Example 8B (100 mg) in methanol (2 mL) was treated with 2.0 M methylamine in methanol (0.75 mL) and stirred overnight. The solvent was evaporated and the crude purified by flash chromatography on silica gel (10% methanol/methylene chloride) to provide 41 mg of the title compound as a white solid.

mp >260 °C;

^1H NMR (300 MHz, DMSO-d_6) δ 1.91 (m, 2H), 2.23 (t, 2H), 2.55 (m, 2H), 2.80 (s, 3H), 4.00 (q, 2H), 4.70 (s, 1H), 7.19 (m, 2H), 7.44 (d, 2H), 9.83 (s, 1H);

MS (ESI+) m/z 391 $(M+H)^+$;

MS (ESI-) m/z 389 $(M-H)^-$;

Anal. Calcd for $C_{18}H_{16}BrFN_2O_2$: C, 55.26; H, 4.12; N, 7.16. Found: C, 54.97; H, 4.15; N, 6.90.

Example 9

9-(3-bromo-4-fluorophenyl)-2-ethyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The product from Example 8B (0.35 g) in methanol (2 mL) was treated with 2.0 M ethylamine in methanol (2.35 mL) and stirred overnight. The solvents were evaporated and the crude purified by flash chromatography on silica gel (10% methanol/methylene chloride). The product was triturated with ether/methanol/methylene chloride to provide 138 mg of the title compound as a white solid.

mp 241-247 °C

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02 (t, 3H), 1.91 (m, 2H), 2.23 (m, 2H), 2.56 (m, 2H), 3.21 (q, 2H), 4.00 (q, 2H), 4.70 (s, 1H), 7.19 (m, 2H), 7.42 (d, 1H), 9.83 (s, 1H);
MS (ESI+) m/z 405 $(M+H)^+$;
MS (ESI-) m/z 403 $(M-H)^-$;
Anal. Calcd for $C_{19}H_{18}BrFN_2O_2$: C, 56.31; H, 4.48; N, 6.91. Found: C, 55.95; H, 4.44; N, 6.84.

Example 10

9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The product from Example 8B (100 mg) was heated to 180 °C in an oil bath for 1 hour and then allowed to cool to ambient temperature. The residue was triturated with acetone, collected, washed with acetone and dried to provide 40 mg of the title compound as a pink solid.
mp >260 °C;
^{1}H NMR (300 MHz, DMSO-d_6) δ 1.91 (m , 2H), 2.25 (m , 2H), 2.58 (m, 2H), 4.68 (s, 1H), 4.90 (q, 2H), 7.23 (m, 2H), 7.44 (d, 1H), 10.19 (s, 1H);
MS (ESI+) m/z 378 $(M+H)^+$;
MS (ESI-) m/z 376 $(M-H)^-$;
Anal. Calcd for $C_{17}H_{13}BrFNO_3$: C, 53.99; H, 3.46; N, 3.70. Found: C, 53.91; H, 3.46; N, 3.58.

Example 11

9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The product from Example 8B (0.40 g) in methanol (35 mL) was treated with ammonia (35 mL) at ambient temperature for 20 hours in a high pressure bomb. The solvent was evaporated and the precipitate collected, washed with 10% methanol/methylene chloride, water, and dried under vacuum at 90 °C overnight to provide 93 mg of the title compound as a gray powder.
mp >260 °C;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90 (m, 2H), 2.25 (m, 2H), 2.55 (m, 2H), 3.92 (q, 2H), 4.70 (s, 1H), 7.19 (m, 2H), 7.44 (m, 2H), 9.78 (s, 1H);

MS (ESI+) m/z 377 $(M+H)^+$;

MS (ESI-) m/z 375 $(M-H)^-$;

Anal. Calcd for $C_{17}H_{14}BrFN_2O_2 \cdot 0.6\ H_2O$: C, 52.62; H, 3.95; N, 7.22. Found: C, 52.29; H, 3.76; N, 7.38.

Example 12

8-(3-bromo-4-fluorophenyl)-2-[2-(4-morpholinyl)ethyl]-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione hydrochloride

2-(4-Morpholino)ethylamine was substituted for methylamine and processed as described in Example 3C to provide the title compound as a white solid. The free amine (80 mg) was dissolved in methyl alcohol and treated with hydrochloric acid (1M in diethyl ether, 10 equiv). The reaction mixture was stirred at ambient temperature for 30 minutes. After removal of the volatiles, the residue was triturated with diethyl ether to provide the title compound (82 mg) as a brown solid.

MS (ESI(+)) m/z 476 $(M+H)^+$;

MS (ESI(-)) m/z 474 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (t, 2H), 2.68 (m, 2H), 3.0-4.0 (m, 8H), 4.22 (q, 2H), 4.59 (s, 1H), 7.25 (m, 2H), 7.51 (d, 1H), 10.28 (br s, 1H), 10.61 (s, 1H);

Anal. Calcd for $C_{22}H_{24}BrClFN_3O_3 \cdot 0.65\ CH_2Cl_2 \cdot 2.5\ H_2O$: C, 44.38; H, 4.98; N, 6.85; Cl, 13.32. Found: C,44.01; H, 5.04; N, 7.02; Cl, 13.57.

Example 13

8-(3-bromo-4-fluorophenyl)-2-[2-(dimethylamino)ethyl]-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione hydrochloride

2-Dimethylaminoethylamine was substituted for methylamine and processed as described in Example 3C to provide the title compound as a white solid. The free amine was dissolved in methyl alcohol and treated with hydrochloric acid (1M in diethyl ether,

10 equiv). The reaction mixture was stirred at ambient temperature for 30 minutes. After removal of the volatiles, the residue was triturated with diethyl ether to provide the title compound (75 mg) as a brown solid.

MS (ESI(+)) m/z 434 $(M+H)^+$;

MS (ESI(-)) m/z 432 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (t, 2H), 2.49 (s, 6H), 2.55-2.80 (m, 4H), 3.48 (m, 2H), 4.17 (s, 2H), 4.59 (s, 1H), 7.23 (d, 2H), 7.48 (d, 1H), 9.43 (br s, 1H), 10.53 (s, 1H);

Anal. Calcd for $C_{20}H_{22}BrClFN_3O_2 \cdot 0.2\ CH_2Cl_2 \cdot 1.8\ H_2O$: C, 46.64; H, 5.04; N, 8.08; Cl, 10.09. Found: C,46.26; H, 5.21; N, 7.74; Cl, 9.88.

Example 14

9-(3-bromo-4-fluorophenyl)-2-(2-methoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

2-Methoxyethylamine was substituted for methylamine and processed as described in Example 8C to provide the title compound as a white solid.

mp 206-208 °C;

MS (ESI(-)) m/z 433 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.92 (m, 2H), 2.23 (t, 2H), 2.55 (m, 2H), 3.22 (s, 3H), 3.32 (t, 2H), 3.39 (m, 2H), 4.05 (q, 2H), 4.70 (s, 1H), 7.20 (m, 2H), 7.42 (d, 1H), 9.83 (s, 1H);

Anal. Calcd for $C_{20}H_{20}BrFN_2O_3$: C, 55.19; H, 4.63; N, 6.44. Found: C, 54.86; H, 4.44; N, 6.06.

Example 15

(9R)-9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

Example 15A

4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylic acid

Boron trichloride (1M in methylene chloride, 200 mL) was added to a solution of the product from Example 8A (19.7 g, 50 mmol) in 50 mL of methylene chloride cooled in an ice bath. The reaction mixture was stirred overnight at ambient temperature and then was diluted with 1000 mL of ice-water and 750 mL of ethyl acetate. After the addition of ethyl acetate, a fine solid was formed, collected, washed with additional ethyl acetate and dried under vacuum at 90 °C to provide the title compound (16.9 g, 89%) as a white powder.

mp 225-228 °C;

MS (ESI(+)) m/z 380 $(M+H)^+$;

MS (ESI(-)) m/z 378 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.70-1.95 (m, 2H), 2.20 (t, 2H), 2.30 (s, 3H), 2.45 (m, 2H), 4.87 (s, 1H), 7.13 (m, 1H), 7.20 (t, 1H), 7.36 (d, 1H), 9.14 (s, 1H), 11.8 (br s, 1H);

Anal. Calcd for $C_{17}H_{15}BrFNO_3$: C, 53.70; H, 3.98; N, 3.68. Found: C, 53.43; H, 3.92; N, 3.56.

Example 15B

(2R)-({[4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinyl]carbonyl}oxy)(phenyl)ethanoic acid

To a solution of Example 15A (16.9 g, 44.5 mmol) in N,N-dimethylformamide (150 mL) at -10 °C was added thionyl chloride (5.29 g, 44.5 mmol). The reaction mixture was stirred at -10 °C for 1.5 hours. (R)-mandelic acid (6.77 g, 44.5 mmol) was added, followed by the addition of triethylamine (4.5 g, 44.5 mmol). The reaction mixture was kept at -10 °C for another 2 hours and at ambient temperature for an hour before it was quenched with ethyl acetate:diethyl ether (1:2) and water. The organic layer was dried, filtered, and concentrated to provide the crude diastereomeric mixture (20 g). The title compound was isolated as the more polar diastereomer after flash chromatography (silica, methyl alcohol:methylene chloride:acetic acid, 10:90:0.5) as yellow solid.

MS (ESI(+)) m/z 514 $(M+H)^+$;

MS (ESI(-)) m/z 512 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.70-1.81 (m, 1H), 1.85-1.94 (m, 1H), 2.20 (m, 2H), 2.34 (s, 3H), 2.48 (m, 2H), 4.87 (s, 1H), 7.13-7.28 (m, 3H), 7.38-7.45 (m, 5H), 9.37 (s, 1H);

Anal. Calcd for $C_{25}H_{21}BrFNO_5$: C, 58.38; H, 4.12; N, 2.72. Found: C, 57.93; H, 4.47; N, 2.33.

Example 15C

methyl (4R)-4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate

The product from Example 15B (257 mg, 0.5 mmol) was dissolved in methyl alcohol (50 mL). Metallic sodium (0.58 g, 25 mmol) was added, and the reaction mixture was refluxed overnight. After concentration, the residue was treated with hydrochloric acid (2M) to pH 7, and diluted with water (50 mL). After being allowed to cool, the mixture was extracted several times with methylene chloride. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to provide the title compound as a white foamy solid (153 mg, 84%).

Example 15D

(9R)-9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The product from Example 15C was processed as described in Example 8C to provide the title compound as a white powder.

MS (ESI(+)) m/z 391 $(M+H)^+$;

MS (ESI(-)) m/z 389 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.91 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 2.79 (s, 3H), 4.02 (q, 2H), 4.70 (s, 1H), 7.19 (m, 2H), 7.42 (d, 1H), 9.82 (s, 1H);

Anal. Calcd for $C_{18}H_{16}BrFN_2O_2$ 0.4 CH_2Cl_2: C, 51.97; H, 3.98; N, 6.59. Found: C, 51.95; H, 3.89; N, 6.60.

Example 16

(9R)-9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The product from Example 15C was processed as described in Example 10 to provide the title compound as a brown solid.

MS (APCI-) m/z 376 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.92 (m, 2H), 2.25 (m, 2H), 2.57 (m, 2H), 4.68 (s, 1H), 4.88 (q, 2H), 7.23 (m, 2H), 7.44 (d, 1H), 10.18 (s, 1H);

Anal. Calcd for $C_{17}H_{13}BrFNO_3$: C, 53.99 ; H, 3.46; N, 3.70. Found: C, 54.10; H, 3.69; N, 3.88.

Example 17

(9R)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The product from Example 15C was processed as described in Example 11 to provide the title compound as a yellow powder.

MS (APCI-) m/z 375 $(M-H)^-$, 411 $(M+Cl^-)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 3.93 (q, 2H), 4.70 (s, 1H), 7.20 (m, 2H), 7.42 (d, 1H), 7.47 (s, 1H), 9.80 (s, 1H);

Anal. Calcd for $C_{17}H_{14}BrFN_2O_2.0.5\ H_2O$: C, 52.87; H, 3.91; N, 7.25. Found: C, 52.87; H, 3.80; N, 7.21.

Example 18

(9S)-9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

Example 18A

4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylic acid

Boron trichloride (1 M in methylene chloride, 200 mL) was added to a solution of the product from Example 8A (19.7 g, 50 mmol) in 50 mL of methylene chloride cooled in an ice bath. The reaction mixture was stirred overnight at ambient temperature and then diluted with 1000 mL of ice-water and 750 mL of ethyl acetate. After the addition of ethyl acetate, a fine solid was formed, collected, washed with additional ethyl acetate and dried under vacuum at 90 °C to provide the title compound (16.9 g, 89%) as a white powder.

mp 225-228 °C;

MS (ESI(+)) m/z 380 $(M+H)^+$;

MS (ESI(-)) m/z 378 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.70-1.95 (m, 2H), 2.20 (t, 2H), 2.30 (s, 3H), 2.45 (m, 2H), 4.87 (s, 1H), 7.13 (m, 1H), 7.20 (t, 1H), 7.36 (d, 1H), 9.14 (s, 1H), 11.8 (br s, 1H);

Anal. Calcd for $C_{17}H_{15}BrFNO_3$: C, 53.70; H, 3.98; N, 3.68. Found: C, 53.43; H, 3.92; N, 3.56.

Example 18B

(2R)-({[4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinyl]carbonyl}oxy)(phenyl)ethanoic acid

To a solution of the product from Example 18A (16.9 g, 44.5 mmol) in N,N-dimethylformamide (150 mL) at -10 °C was added thionyl chloride (5.29 g, 44.5 mmol). The reaction mixture was stirred at -10 °C for 1.5 hours. (R)-mandelic acid (6.77 g, 44.5 mmol) was added, followed by the addition of triethylamine (4.5 g, 44.5 mmol). The reaction mixture was kept at -10 °C for another 2 hours and at ambient temperature for an hour, before it was quenched with ethyl acetate:diethyl ether (1:2), and water. The organic layer was dried, filtered, and concentrated to provide the crude diastereomeric mixture (20 g). The title compound was isolated as the less polar diastereomer after flash chromatography (silica, methyl alcohol:methylene chloride:acetic acid, 10:90:0.5) as a yellow solid.

MS (ESI(+)) m/z 514 $(M+H)^+$;

MS (ESI(-)) m/z 512 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.70-1.81 (m, 1H), 1.85-1.94 (m, 1H), 2.20 (m, 2H), 2.34 (s, 3H), 2.48 (m, 2H), 4.87 (s, 1H), 7.13-7.28 (m, 3H), 7.38-7.45 (m, 5H), 9.37 (s, 1H);

Anal. Calcd for $C_{25}H_{21}BrFNO_5$ 0.2 C_7H_8: C, 59.52; H, 4.28; N, 2.63. Found: C, 59.90; H, 4.57; N, 2.35.

Example 18C

methyl (4S)-4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate

The product from Example 18B (257 mg, 0.5 mmol) was dissolved in methyl alcohol (50 mL). Metallic sodium (0.58 g, 25 mmol) was added, and the reaction mixture was refluxed overnight. After concentration, the residue was treated with hydrochloric acid (2 M) to pH 7, and diluted with water (50 mL). After being allowed to cool, the mixture was extracted several times with methylene chloride. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to provide the title compound as a white foamy solid (153 mg, 84%). Absolute stereochemistry was determined by X-ray crystallographic analysis.

Example 18D

(9S)-9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The product from Example 18C was processed as described in Example 10 to provide the title compound as a light pink powder.

MS (ESI(-)) m/z 376 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.91 (m, 2H), 2.26 (m, 2H), 2.58 (m , 2H), 4.68 (s, 1H), 4.89 (q, 2H), 7.23 (m, 2H), 7.44 (d, 1H), 10.17 (s, 1H);

Anal. Calcd for $C_{17}H_{13}BrFNO_3$.0.2 H_2O: C, 53.48; H, 3.54; N, 3.67. Found: C, 53.18; H, 3.92; N, 3.46.

Example 19

(9S)-9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The product from Example 18C was processed as described in Example 8C to provide the title compound as a pale yellow solid.

MS (ESI(+)) m/z 391 $(M+H)^+$;

MS (ESI(-)) m/z 389 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90 (m, 2H), 2.24 (m, 2H), 2.55 (m, 2H), 2.78 (s, 3H), 4.02 (q, 2H), 4.69 (s, 1H), 7.18 (m, 2H), 7.43 (d, 1H), 9.80 (s, 1H);

Anal. Calcd for $C_{18}H_{16}BrFN_2O_2$: C, 55.26; H, 4.12; N, 7.16. Found: C, 54.99; H, 4.08; N, 7.03.

Example 20

(9S)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The product from Example 18C was processed as described in Example 11 to provide the title compound as a beige solid.

MS (ESI(+)) m/z 377 $(M+H)^+$;

MS (ESI(-)) m/z 375 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 3.93 (q, 2H), 4.69 (s, 1H), 7.19 (m, 2H), 7.42 (d, 1H), 7.48 (s, 1H), 9.80 (s, 1H);

Anal. Calcd for $C_{17}H_{14}BrFN_2O_2.0.4\ CH_2Cl_2$: C, 50.83; H, 3.63; N, 6.81. Found: C, 50.67; H, 3.80; N, 6.75.

Example 21

9-(3-cyanophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

3-Cyanobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 8C to provide the title compound as a yellow solid.

MS (ESI +) m/z 320 $(M+H)^+$;

MS (ESI -) m/z 318 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88-1.94 (m, 2H), 2.21-2.26 (m, 2H), 2.54-2.57 (m, 2H), 2.78 (s, 3H), 4.00 (q, 2H), 4.74 (s, 1H), 7.42 (t, 1H), 7.52-7.58 (m, 3H), 9.83 (s, 1H);

Anal. Calcd for $C_{19}H_{17}N_3O_2.0.6\ H_2O$: C, 69.33; H, 5.27; N, 12.77. Found: C, 68.87; H, 5.71; N, 12.42.

Example 22

8-(3-bromo-4-fluorophenyl)-6-methyl-2,3,4,5,6,8-hexahydro-7H-pyrrolo[3,4-b]thieno[2,3-e]pyridin-7-one 1,1-dioxide

Example 22A

methyl 7-(3-bromo-4-fluorophenyl)-5-methyl-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate 1,1-dioxide

3-Bromo-4-fluorobenzaldehyde (2.03 g, 10 mmol), 3-aminocrotonate (1.15 g, 10 mmol) and tetrahydrothiophene-3-oxo-1,1-dioxide prepared as described in (J. Heterocycl. Chem., v. 27 pp. 1453 (1990)),(1.29 g, 9.6 mmol) were suspended in methyl alcohol (30 mL). The reaction mixture was stirred in a sealed tube at 65 °C overnight. The white precipitate formed (hemiaminal intermediate) was filtered and washed with acetone. That intermediate was suspended again in methyl alcohol and treated with hydrochloric acid (1M in diethyl ether, 10 mL). The reaction mixture was refluxed for 2 hours. After concentration, the white residue was triturated with diethyl ether and filtered to provide the title compound (2.88 g, 72%) as a white solid.

mp 232-234 °C;

MS (ESI(-)) m/z 416 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.75-3.05 (m, 2H), 3.28-3.35 (m, 2H), 3.52 (s, 3H), 4.87 (s, 1H), 7.19 (m, 1H), 7.26 (t, 1H), 7.48 (d, 1H), 9.50 (s, 1H);

Anal. Calcd for $C_{16}H_{15}BrFNO_4S$: C, 46.17; H, 3.63; N, 3.36. Found: C, 46.13; H, 3.78; N, 3.27.

Example 22B

8-(3-bromo-4-fluorophenyl)-6-methyl-2,3,4,5,6,8-hexahydro-7H-pyrrolo[3,4-b]thieno[2,3-e]pyridin-7-one 1,1-dioxide

The product from Example 22A (104 mg, 0.25 mmol) was dissolved in chloroform (2 mL) and treated with pyridinium tribromide (58 mg, 0.275 mmol) at -10 °C. The reaction mixture was warmed up to ambient temperature gradually, and stirred for 2 hours. Methylamine (2.0M in methyl alcohol, 1.4 mL) was added to the reaction mixture. After stirring at ambient temperature overnight, the reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica, 7.5% methyl alcohol-methylene chloride) to provide the title compound (26 mg, 25%) as a light yellow powder.

MS (ESI(+)) m/z 413 $(M+H)^+$;

MS (ESI(-)) m/z 411 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.78 (s, 3H), 2.82-3.10 (m , 2H), 3.36 (t, 2H), 4.04 (q, 2H), 4.78 (s, 1H), 7.27 (m , 2H), 7.48 (d, 1H), 9.96 (s, 1H).

Example 23

9-(3-bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

3-Bromo-4-fluorobenzaldehyde (1 mmol, 203 mg), piperidine-2,4-dione, prepared using a similar procedure as described in (Lowe, G. and Yeung, H.W., J. Chem. Soc. Perkin I, (1973) 2907-2910, from β-alanine ethyl ester hydrochloride and ethyl malonyl chloride), (1 mmol, 113 mg) and 3-amino-2-cyclopenten-1-one (1 mmol, 97 mg) were suspended in ethyl alcohol (5 mL). The reaction mixture was heated in a sealed tube at 80 °C for a period of 48 hours. The precipitate formed was collected by filtration, washed with cold ethyl alcohol and dried under vacuum to provide the title compound (122 mg, 32%).

MS (APCI+) m/z 377 $(M+H)^+$;

^{1}H NMR (DMSO-d_6) δ 2.25 (t, 2H), 2.40-2.70 (m, 4H), 3.15-3.35 (m, 2H), 4.70 (s, 1H), 7.07 (bs, 1H), 7.17-7.22 (m, 2H), 7.42 (dd, 1H), 9.83 (s, 1H);

Anal. Calcd for $C_{17}H_{14}N_2O_2FBr$: C, 54.13; H, 3.74; N, 7.43. Found: C, 53.91; H, 3.82; N, 7.42.

Example 24

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydrobenzo[b][1,6]naphthyridine-1,9(2H,5H)-dione

3-Bromo-4-fluorobenzaldehyde (1 mmol, 203 mg), piperidine-2,4-dione (1 mmol, 113 mg) and 3-amino-2-cyclohexen-1-one (1 mmol, 111 mg) were suspended in ethyl alcohol (5 mL). The reaction mixture was heated in a sealed tube at 50 °C for a period of 72 hours. The precipitate formed was collected by filtration, washed with cold ethyl alcohol and dried under vacuum to provide the title compound (218 mg, 56%).

MS (ESI+) m/z 391 $(M+H)^+$;

^1H NMR (DMSO-d_6) δ 1.70-1.97 (m, 2H), 2.15-2.25 (m, 2H), 2.36-2.59 (m, 4H), 3.13-3.23 (m, 2H), 4.90 (s, 1H), 7.00 (bs, 1H), 7.15-7.20 (m, 2H), 7.39 (dd, 1H), 9.28 (s, 1H);

Anal. Calcd for $C_{18}H_{16}N_2O_2FBr$: C, 55.26; H, 4.12; N, 7.16. Found: C, 55.06; H, 4.32; N, 7.14.

Example 25

(9S)-9-(4-fluoro-3-iodophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

Example 25A

(3-amino-4-fluorophenyl)methanol

3-Amino-4-fluorobenzoic acid (15 g, 97 mmol) in tetrahydrofuran at 0 °C was treated with 1.0 M borane-tetrahydrofuran complex (50 mL), stirred overnight at room temperature, treated with an additional 130 mL of 1.0 M borane-tetrahydrofuran complex, stirred 10 hours, quenched by the addition of methanol, stirred 3 hours at room temperature, concentrated and partitioned between aqueous sodium bicarbonate/methylene chloride. The methylene chloride layer was dried (sodium sulfate), filtered and

concentrated. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexane 1:1) to provide 7.0 g of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (s, 2H), 6.67 (br m, 1H), 6.81 (d, 1H), 6.95 (t, 1H).

Example 25B

(4-fluoro-3-iodophenyl)methanol

The product from Example 25A (7.0 g, 50 mmol) in water (100 mL) at 0 °C was treated slowly with concentrated sulfuric acid (30 mL) at a rate to maintain the temperature below 10 °C and then treated dropwise with an aqueous solution of sodium nitrite (3.45 g, 50 mmol). This solution was then added to a solution of potassium iodide (8.13 g, 50 mmol) in water (15 mL), heated to 60 °C for 2 hours, cooled and extracted with methylene chloride. The methylene chloride layer was washed with 10% sodium hydroxide, washed with 1 M sodium thiosulfate, washed with 10% hydrochloric acid, washed with aqueous sodium bicarbonate, dried (sodium sulfate), filtered and concentrated. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexane 7:3) to provide 6.4 g of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (t, 1H), 4.66 (d, 2H), 7.05 (t, 1H), 7.60 (d, 1H), 7.78 (dd, 1H).

Example 25C

4-fluoro-3-iodobenzaldehyde

The product from Example 25B (6.4 g, 26 mmol) in chloroform (300 mL) was treated with manganese dioxide (4.5 g, 50 mmol), stirred overnight, treated with an additional portion of manganese dioxide (2.25 g), stirred overnight, filtered and concentrated. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexane 1:4) to provide 1.9 g of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, 1H), 7.89 (m, 1H), 8.32 (dd, 1H), 9.91 (s, 1H).

Example 25D

(9S)-9-(4-fluoro-3-iodophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

4-Fluoro-3-iodobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 18C to provide the title compound as a white powder.

MS (ESI(+)) m/z 426 $(M+H)^+$;

MS (ESI(-)) m/z 424 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85-1.95 (m, 2H), 2.22-2.27 (m, 2H), 2.56-2.59 (m, 2H), 4.63 (s, 1H), 4.89 (q, 2H), 7.12 (t, 1H), 7.20 (dt, 1H), 7.60 (dd, 1H), 10.18 (br s, 1H);

Anal. Calcd for $C_{17}H_{13}FINO_3$: C, 48.02; H, 3.08; N, 3.29. Found: C, 47.86; H, 3.35; N, 3.22.

Example 26

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydropyrido[4,3-b][1,6]naphthyridine-1,9(2H,5H)-dione

A mixture of 3-bromo-4-fluorobenzaldehyde (1 mmol, 203 mg) and piperidine-2,4-dione (2 mmol, 226 mg) in ethyl alcohol (5 mL) was treated with ammonia (2 M in ethyl alcohol, 1 mmol, 0.5 mL). The reaction mixture was heated in a sealed tube at 70 °C for a period of 48 hours. The precipitate formed was collected by filtration, washed with cold ethyl alcohol and dried under vacuum to provide the title compound (150 mg, 38%).

MS (APCI+) m/z 392 $(M+H)^+$;

^{1}H NMR (DMSO-d_6) δ 2.32-2.56 (m, 4H), 3.12-3.22 (m, 4H), 4.93 (s, 1H), 6.94 (bs, 2H), 7.18-7.22 (m, 2H), 7.42 (dd, 1H), 8.98 (s, 1H);

Anal. Calcd for $C_{17}H_{15}N_3O_2FBr$: C, 52.06; H, 3.85; N, 10.71. Found: C, 52.09; H, 4.11; N, 10.36.

Example 27

9-(3-bromo-4-fluorophenyl)-7-methyl-3,4,5,6,7,9-hexahydropyrrolo[3,4-b]thiopyrano[2,3-e]pyridin-8(2H)-one 1,1-dioxide

Example 27A

methyl 8-(3-bromo-4-fluorophenyl)-6-methyl-3,4,5,8-tetrahydro-2H-thiopyrano[3,2-b]pyridine-7-carboxylate 1,1-dioxide

3-Bromo-4-fluorobenzaldehyde (2.03 g, 10 mmol), 3-aminocrotonate (1.15 g, 10 mmol) and tetrahydrothiopyran-3-one-1,1-dioxide prepared as described in (J. Heterocycl. Chem. (1990), 27, 1453) (1.48 g, 10 mmol) were suspended in methyl alcohol (30 mL). The reaction mixture was stirred in a sealed tube at 65 °C overnight. The precipitate formed was collected and washed with acetone to provide the desired product (3.11 g, 72%) as a white powder.

mp 255 °C;

MS (ESI(-)) m/z 430 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (m, 2H), 2.27 (s, 3H), 2.43-2.55 (m, 2H), 3.14-3.22 (m, 2H), 3.58 (s, 3H), 4.97 (s, 1H), 7.19 (m, 1H), 7.25 (t, 1H), 7.36 (d, 1H), 9.12 (s, 1H);

Anal. Calcd for $C_{17}H_{17}BrFNO_4S$: C, 47.45; H, 3.98; N, 3.26. Found: C, 47.40; H, 4.11; N, 3.21.

Example 27B

9-(3-bromo-4-fluorophenyl)-7-methyl-3,4,5,6,7,9-hexahydropyrrolo[3,4-b]thiopyrano[2,3-e]pyridin-8(2H)-one 1,1-dioxide

The product from Example 27A (107.5 mg, 0.25 mmol) was dissolved in chloroform (2 mL) and treated with pyridine (0.30 mmol). The reaction mixture was cooled to -10 °C, and then pyridinium tribromide (98 mg, 0.275 mmol) was added. After stirring at -10 °C for 1 hour and at ambient temperature for another 1 hour, the reaction mixture was treated with hydrochloric acid (1 M, 2 mL), and extracted with chloroform (3 x 3 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to give a white foamy solid. This solid was dissolved in methyl alcohol (2 mL) and treated with methylamine (2 M in methyl alcohol, 1.25 mL). The reaction mixture was stirred at ambient temperature overnight. Following concentration, the residue was flash chromatographed (silica gel, 10% methyl alcohol-methylene chloride) to provide the title compound (49 mg, 46%) as a light yellow powder.

MS (ESI(+)) m/z 427 $(M+H)^+$;

MS (ESI(-)) m/z 425 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18-2.24 (m, 2H), 2.58 (m, 2H), 2.78 (s, 3H), 3.16-3.22 (m, 2H), 3.98 (q, 2H), 4.86 (s, 1H), 7.26 (m, 2H), 7.43 (d, 1H), 9.60 (s, 1H);

Anal. Calcd for $C_{17}H_{16}BrFN_2O_3S$: C, 47.79; H, 3.77; N, 6.56. Found: C, 47.31; H, 4.03; N, 6.31.

Example 28

9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide

The product from Example 27A (860 mg, 2 mmol) was dissolved in chloroform (15 mL) and treated with pyridine (2.4 mmol). The reaction mixture was cooled to -10 °C, and then pyridinium tribromide (782 mg, 2.2 mmol) was added. After stirring at -10 °C for 1 hour and at ambient temperature for another 1 hour, the reaction mixture was treated with hydrochloric acid (1 M, 15 mL), and extracted with chloroform (3 x 15 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to give a white foamy solid. This solid was heated at 140 °C for 1 hour. Flash chromatography (silica gel, 10% methyl alcohol-methylene chloride) provided the title compound (345 mg, 63%) as a white solid.

MS (ESI(-)) m/z 412 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18-2.22 (m, 2H), 2.56-2.61 (m, 2H), 3.18-3.23 (m, 2H), 4.86 (s, 1H), 4.87 (q, 2H), 7.28 (m, 2H), 7.47 (d, 1H), 10.03 (br s, 1H);

Anal. Calcd for $C_{16}H_{13}BrFNO_4S$: C, 46.39; H, 3.16; N, 3.38. Found: C, 46.65; H, 3.46; N, 3.31.

Example 29

(8R)-8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione

The enantiomerically pure title compound was obtained after chiral HPLC resolution (Chiralcel OD, 4.6x250mm, hexane:ethanol, 90:10) of the corresponding racemate prepared as described in Example 3C.

light yellow crystalline solid;

MS (ESI(+)) m/z 377 $(M+H)^+$;

MS (ESI(-)) m/z 375 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (t, 2H), 2.55-2.67 (m, 2H), 2.80 (s, 3H), 4.08 (q, 2H), 4.56 (s, 1H), 7.21 (m, 2H), 7.44 (d, 1H);

Anal. Calcd for $C_{17}H_{14}BrFN_2O_2$: C, 54.13; H, 3.74; N, 7.43. Found: C, 53.96; H, 3.89; N, 7.17.

Example 30

9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide

Example 30A

(1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 9-(3-bromo-4-fluorophenyl)-8-oxo-2,3,4,6,8,9-hexahydro-5H-furo[3,4-b]thiopyrano[2,3-e]pyridine-5-carboxylate 1,1-dioxide

To a suspension of the product from Example 28 (1.02 g, 2.46 mmol) in tetrahydrofuran (10 mL) kept at 0 °C under nitrogen was added slowly potassium t-butoxide (1 M in tetrahydrofuran, 2.46 mL). The reaction mixture was allowed to warm up to ambient temperature for a period of 10 minutes and then cooled back to 0 °C. Then a solution of 8-phenylmenthol chloroformate prepared from (-)-8-phenylmenthol as described in (Reference: Yamamoto, Y., J. Amer. Chem. Soc. (1992), 114, 121-125) (0.727 g, 2.46 mmol) in tetrahydrofuran (25 mL) was added. The reaction mixture was allowed to warm up to ambient temperature again and stirred for another two hours. Then

it was poured into an aqueous saturated sodium bicarbonate solution and extracted with a mixture of diethyl ether and ethyl acetate (4:1, 3 x 25 mL). The layers were separated and the organic layer was dried over magnesium sulfate, filtered and concentrated. Flash column chromatography (silica, diethyl ether:hexane, 85:15) of the residue provided the less polar diastereomer (750 mg) and the more polar diastereomer (655 mg).

Example 30B

9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide

A solution of the less polar diastereomer from Example 30A (639 mg) in methyl alcohol (10 mL) was treated with a 25% sodium methoxide solution in methyl alcohol (three drops) under nitrogen. The solution slowly turned into a suspension. After completion of the reaction (evidenced by TLC) a few drops of acetic acid were added resulting in the formation of a precipitate that was isolated by filtration and air dried to provide the title compound (210 mg, 53% yield) as a white solid.

MS (ESI(-)) m/z 412 $(M-H)^-$;

^1H NMR (300 MHz, DMSO-d_6) δ 2.18-2.22 (m, 2H), 2.56-2.61 (m, 2H), 3.18-3.23 (m, 2H), 4.86 (s, 1H), 4.87 (q, 2H), 7.28 (m, 2H), 7.47 (d, 1H), 10.03 (br s, 1H);

Anal. Calcd for $C_{16}H_{13}BrFNO_4S$: C, 46.39; H, 3.16; N, 3.38. Found: C, 46.55; H, 3.16; N, 3.23.

Example 31

(8S)-8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione

The enantiomerically pure title compound was obtained after chiral HPLC resolution (Chiralcel OD, 4.6x250mm, hexane:ethanol, 90:10) of the corresponding racemate prepared as described in Example 3C. Absolute stereochemistry was determined by X-ray crystallographic analysis.

light yellow crystalline solid:

MS (ESI(+)) m/z 377 $(M+H)^+$;

MS (ESI(-)) m/z 375 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (t, 2H), 2.55-2.67 (m, 2H), 2.80 (s, 3H), 4.08 (q, 2H), 4.56 (s, 1H), 7.21 (m, 2H), 7.44 (d, 1H);

Anal. Calcd for $C_{17}H_{14}BrFN_2O_2.0.5\ H_2O$: C, 52.87; H, 3.91; N, 7.25. Found: C, 53.16; H, 4.13; N, 6.78.

Example 32

9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide

The more polar diastereomer from Example 30A (655 mg) was processed as described in Example 30B to provide the title compound as a white solid (290 mg, 72%).

MS (ESI(-)) m/z 412 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18-2.22 (m, 2H), 2.56-2.61 (m, 2H), 3.18-3.23 (m, 2H), 4.86 (s, 1H), 4.87 (q, 2H), 7.28 (m, 2H), 7.47 (d, 1H), 10.03 (br s, 1H);

Anal. Calcd for $C_{16}H_{13}BrFNO_4S$: C, 46.39; H, 3.16; N, 3.38. Found: C, 46.39; H, 3.24; N, 3.33.

Example 33

9-(3-bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

2-Ethoxyethylamine was substituted for methylamine and processed as described in Example 8C to provide the title compound.

MS (APCI(+)) m/z 451 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.82-1.97 (m, 2H), 2.20-2.30 (m, 2H), 2.50-2.65 (m, 2H), 3.35-3.45 (m, 6H), 4.08 (q, 2H), 4.72 (s, 1H), 7.15-7.25 (m, 2H), 7.45 (m, 1H), 9.80 (s, 1H).

Example 34

(9R)-9-(3-bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The enantiomerically pure title compound was obtained as described in Example 8C using the product from Example 18C, and substituting 2-ethoxyethylamine for methylamine.

MS (APCI(+)) m/z 451 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (t, 3H), 1.82-1.98 (m, 2H), 2.20-2.30 (m, 2H), 2.50-2.65 (m, 2H), 3.35-3.50 (m, 6H), 4.06 (q, 2H), 4.70 (s, 1H), 7.15-7.25 (m, 2H), 7.45 (m, 1H), 9.79 (s, 1H).

Example 35

(9S)-9-(3-bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The enantiomerically pure title compound was obtained as described in Example 8C using the product from Example 15C and substituting 2-ethoxyethylamine for methylamine. yellow solid:

MS (ESI(+)) m/z 449 $(M+H)^+$;

MS (ESI(-)) m/z 447 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.6 (t, 3H), 1.85-1.94 (m, 2H), 2.22-2.28 (m, 2H), 2.53-2.58 (m, 2H), 3.34-3.45 (m, 6H), 4.18 (q, 2H), 4.70 (s, 1H), 7.17-7.22 (m, 2H), 7.42 (d, 1H), 9.82 (s, 1H);

Anal. Calcd for $C_{21}H_{22}BrFN_2O_3$: C, 56.14; H, 4.94; N, 6.23. Found: C, 56.43; H, 4.99; N, 5.98.

Example 36

(9S)-9-(3-bromo-4-fluorophenyl)-2-cyclopropyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The enantiomerically pure title compound was obtained as described in Example 8C using the product from Example 15C, and substituting cyclopropylamine for methylamine.

MS (APCI(+)) m/z 419 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.58-0.65 (m, 4H), 1.80-1.98 (m, 2H), 2.05 (s, 1H), 2.20-2.28 (m, 2H), 2.55-2.65 (m, 2H), 3.90 (q, 2H), 4.65 (s, 1H), 7.15-7.22 (m, 2H), 7.45 (m, 1H), 9.80 (s, 1H).

Example 37

9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-b][1,6]naphthyridin-8(4H)-one 1,1-dioxide

A suspension of 3-bromo-4-fluorobenzaldehyde (2.19 mmol, 444 mg), piperidine-2,4-dione (2.19 mmol, 247 mg) and tetrahydrothiophene-3-oxo-1,1-dioxide (2.19 mmol, 293 mg) in ethyl alcohol (10 mL) was treated with ammonium acetate (1.5 equiv, 3.29 mmol) and heated in a sealed tube at 80 °C for a period of 72 hours. The white precipitate formed was collected by filtration. Flash column chromatography (silica gel, methylene chloride:methyl alcohol, 10:1 to 5:1) of that precipitate afforded the title compound (80 mg, 9% yield).

MS (APCI+) m/z 413 $(M+H)^+$;

^{1}H NMR (DMSO-d_6) δ 2.33-2.53 (m, 2H), 2.73-2.86 (m, 2H), 2.94-3.07 (m, 2H), 3.13-3.22 (m, 2H), 4.90 (s, 1H), 7.08 (bs, 1H), 7.19-7.27 (m, 2H), 7.41 (dd, 1H), 9.50 (s, 1H);

Anal. Calcd for $C_{16}H_{14}N_2O_3SFBr$: C, 46.50; H, 3.41; N, 6.78. Found: C, 46.24; H, 3.55; N, 6.72.

Example 38

(9R)-9-(4-fluoro-3-iodophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The product from Example 15C and 4-Fluoro-3-iodobenzaldehyde from Example 25C were processed as described in Example 16 to provide the title compound as a pink powder.

MS (ESI(+)) m/z 426 $(M+H)^+$;

MS (ESI(-)) m/z 424 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85-1.95 (m, 2H), 2.22-2.27 (m, 2H), 2.56-2.59 (m, 2H), 4.63 (s, 1H), 4.89 (q, 2H), 7.12 (t, 1H), 7.20 (dt, 1H), 7.60 (dd, 1H), 10.18 (br s, 1H);

Anal. Calcd for $C_{17}H_{13}FINO_3$: C, 48.02; H, 3.08; N, 3.29. Found: C, 47.92; H, 3.06; N, 3.10.

Example 39

(9R)-9-(3-chloro-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The product from Example 15C and 3-chloro-4-fluorobenzaldehyde were processed as described in Example 16 to provide the title compound as a brown solid.

MS (ESI(+)) m/z 334 $(M+H)^+$;

MS (ESI(-)) m/z 332 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85-1.95 (m, 2H), 2.23-2.29 (m, 2H), 2.55-2.60 (m, 2H), 4.69 (s, 1H), 4.90 (q, 2H), 7.19 (m, 1H), 7.28 (t, 1H), 7.32 (d, 1H), 10.20 (s, 1H) ;

Anal. Calcd for $C_{17}H_{13}ClFNO_3.0.2\ H_2O$: C, 60.53; H, 4.00; N, 4.15. Found: C, 60.29; H, 3.97; N, 4.15.

Example 40

9-(3-chloro-4-fluorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

3-Chloro-4-fluorobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 333 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (m, 2H), 2.45-2.63 (m, 4H), 3.15-3.34 (m, 2H), 4.85 (s, 1H), 7.05 (s, 1H), 7.13-7.35 (m, 3H), 9.95 (s, 1H).

Example 41

9-[4-fluoro-3-(trifluoromethyl)phenyl]-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

4-Fluoro-3-trifluoromethylbenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS(APCI+) m/z 367$(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (m, 2H), 2.35-2.65 (m, 4H), 3.26-3.40 (m, 2H), 4.90 (s, 1H), 7.07 (s, 1H), 7.26-7.43 (m, 3H), 9.80 (s, 1H).

Example 42

9-(4-chloro-3-fluorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

4-Chloro-3-fluorobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 333 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.10 (m, 2H), 2.25-2.70(m, 4H), 3.10-3.35 (m, 2H), 4.80 (s, 1H), 6.95-7.65(m, 4H), 959(s, 1H).

Example 43

9-(3,4-dichlorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

3,4-Dichlorobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 349$(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (m, 2H), 2.25-2.80 (m, 4H), 3.25-3.45 (m, 2H), 4.90(s, 1H), 7.05-7.58(m, 4H), 9.90(s, 1H).

Example 44

9-[4-chloro-3-(trifluoromethyl)phenyl]-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

4-Chloro-3-trifluoromethylbenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 383 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15(m, 2H), 2.20-2.70(m, 4H), 3.10-3.40 (m, 2H), 4.80 (s, 1H), 7.10(s, 1H), 7.40-7.70 (m, 3H), 9.85 (s, 1H).

Example 45

9-(3,4-dibromophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

3,4-Dibromobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 439 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.14 (m, 2H), 2.19-2.75 (m, 4H), 3.15-3.45 (m, 4H), 4.70 (s, 1H), 7.00-7.63 (m, 4H), 9.85 (s, 1H).

Example 46

9-(3-cyanophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

3-Cyanobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 306 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (m, 2H), 2.20-2.70 (m, 4H), 3.15-3.40 (m, 2H), 4.79 (s, 1H), 7.05 (s, 1H), 7.40-7.60 (m, 3H), 9.90 m(s, 1H).

Example 47

9-(5-chloro-2-thienyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

5-Chloro-2-thiophenecarboxaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 321 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20-2.75 (m, 6H), 3.15-3.40 (m, 2H), 4.85 (s, 1H), 6.50 (d, 1H), 6.80 (d, 1H), 7.20 (s, 1H), 9.90 (s, 1H).

Example 48

9-(3-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

3-Nitrobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 326 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (m, 2H), 2.40-2.70 (m, 4H), 3.15-3.40 (m, 2H), 4.85 (s, 1H), 7.05 (s, 1H), 7.50-8.00 (m, 3H), 9.90 (s, 1H).

Example 49

9-(5-nitro-2-thienyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

5-Nitro-2-thiophenecarboxaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 332 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25-2.80 (m, 6H), 3.20-3.45 (m, 2H), 5.00 (s, 1H), 6.90 (d, 1H), 7.25 (s, 1H), 7.90 (d, 1H), 10.05 (s, 1H).

Example 50

9-(5-nitro-3-thienyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione

5-Nitro-3-thiophenecarboxyaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 23 to provide the title compound.

MS (APCI(+)) m/z 332 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (m, 2H), 2.39-2.80 (m, 4H), 3.20-3.40 (m, 2H), 4.80 (s, 1H), 7.18 (s, 1H), 7.59(s, 1H), 7.85 (s, 1H), 9.90 (s, 1H).

Example 51

9-[4-fluoro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

4-Fluoro-3-trifluoromethylbenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 10 to provide the title compound as a white solid.

MS (ESI(+)) m/z 368 $(M+H)^+$;

MS (ESI(-)) m/z 366 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88-1.95 (m, 2H), 2.24-2.28 (m, 2H), 2.55-2.61 (m, 2H), 4.78 (s, 1H), 4.90 (q, 2H), 7.49 (t, 1H), 7.52 (m, 2H), 10.21 (s, 1H);

Anal. Calcd for $C_{18}H_{13}F_4NO_3$: C, 58.86; H, 3.57; N, 3.81. Found: C, 58.71; H, 3.60; N, 3.80.

Example 52

9-(4-chloro-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

4-Chloro-3-nitrobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 10 to provide the title compound as a yellow solid.

MS (ESI(-)) m/z 359 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88-1.96 (m, 2H), 2.25-2.60 (m, 2H), 2.56-2.61 (m, 2H), 4.79 (s, 1H), 4.90 (q, 2H), 7.55 (d, 1H), 7.65 (d, 1H), 7.81 (s, 1H), 10.27 (s, 1H);

Anal. Calcd for $C_{17}H_{13}ClN_2O_5$.0.1 CH_2Cl_2: C, 55.62; H, 3.60; N, 7.59. Found: C, 55.71; H, 3.75; N, 7.40.

Example 53

8-[4-fluoro-3-(2-furyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

The title compound from Example 5 was processed as described in Example 91 to provide the title compound.

MS (ESI (-)) m/z 352 $(M-H)^-$;

^1H NMR (300 MHz, DMSO-d_6) δ 4.71 (s, 1H), 4.91 - 5.07 (m, 4H), 6.67 (m, 1H), 6.85 (t, J=3.4 Hz, 1H), 7.22 (m, 1H), 7.27 (m, 1H), 7.66 (dd, J=7.3, 2.2 Hz, 1H), 7.85 (d, J=2.2 Hz, 1H), 10.71 (s, 1H);

Anal. Calcd for $C_{19}H_{12}FNO_5$.0.3 H_2O: C, 63.62; H, 3.54; N, 3.90. Found: C, 63.53; H, 3.93; N, 3.96.

Example 54

8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 22.5 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(50:33:17) of the corresponding racemate prepared as described in Example 6.

yellow solid:

MS (ESI(+)) m/z 364 $(M+H)^+$;

MS (ESI(-)) m/z 362 $(M-H)^-$;

^1H NMR (300 MHz, DMSO-d_6) δ 2.35 (t, 2H), 2.70 (m, 2H), 4.60 (s, 1H), 4.98 (q, 2H), 7.26 (m, 2H), 7.50 (d, 1H), 10.71 (s, 1H);

Anal. Calcd for $C_{16}H_{11}BrFNO_3$: C, 52.77; H, 3.04; N, 3.85. Found: C, 52.39; H, 3.18; N, 3.75.

Example 55

8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 28 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(50:33:17) of the corresponding racemate prepared as described in Example 6.

yellow solid:

MS (ESI(+)) m/z 364 $(M+H)^+$;

MS (ESI(-)) m/z 362 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (t, 2H), 2.70 (m, 2H), 4.60 (s, 1H), 4.98 (q, 2H), 7.26 (m, 2H), 7.50 (d, 1H), 10.71 (s, 1H);

Anal. Calcd for $C_{16}H_{11}BrFNO_3$: C, 52.77; H, 3.04; N, 3.85. Found: C, 52.54; H, 3.18; N, 3.75.

Example 56

8-[4-fluoro-3-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

4-Fluoro-3-trifluoromethylbenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as in Example 5 to provide the title compound as a white solid.

MS (DCI/NH_3) m/z 373 (100%) $(M+NH_4)$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 4.82 (s, 1H), 4.98 (q, 4H), 7.44 (t, 1H), 7.63 (m, 2H), 10.78 (s, 1H);

Anal. Calcd for $C_{16}H_9F_4NO_4$: C, 54.10; H, 2.55; N, 3.94. Found: C, 53.81; H, 2.65; N, 3.86.

Example 57

9-[4-fluoro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 65 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(75:16.5:8.5) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde.

MS (ESI(+)) m/z 368 $(M+H)^+$;

MS (ESI(-)) m/z 366 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.82-1.98 (m, 2H), 2.23-2.28 (m, 2H), 2.54-2.60 (m, 2H), 4.77 (s, 1H), 4.89 (q, 2H), 7.38 (t, 1H), 7.53 (m, 2H), 10.21 (s, 1H);

Anal. Calcd for $C_{18}H_{13}F_4NO_3$: C, 58.86; H, 3.57; N, 3.81. Found: C, 58.75; H, 3.84; N, 3.62.

Example 58

9-[4-fluoro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 77 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(75:16.5:8.5) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde.

MS (ESI(+)) m/z 368 $(M+H)^+$;

MS (ESI(-)) m/z 366 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.82-1.98 (m, 2H), 2.23-2.28 (m, 2H), 2.54-2.60 (m, 2H), 4.77 (s, 1H), 4.89 (q, 2H), 7.38 (t, 1H), 7.53 (m, 2H), 10.21 (s, 1H);

Anal. Calcd for $C_{18}H_{13}F_4NO_3$: C, 58.86; H, 3.57; N, 3.81. Found: C, 58.70; H, 3.83; N, 3.67.

Example 59

8-(3,4-dichlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

3,4-Dichlorobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as in Example 5 to provide the title compound as a white solid.

MS (DCI/NH_3) m/z 346 (100%) ($M+NH_4$);

^{1}H NMR (300 MHz, DMSO-d_6) δ 4.78 (s, 1H), 4.98 (q, 4H), 7.42 (d, 1H), 7.55 (d, 1H), 7.82 (s, 1H), 10.74 (s, 1H);

Anal. Calcd for $C_{15}H_9Cl_2NO_4.0.25H_20$: C, 52.58; H, 2.79; N, 4.09. Found: C, 52.64; H, 2.60; N, 4.04.

Example 60

8-(4-methyl-3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

4-Methyl-3-nitrobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as in Example 5 to provide the title compound as a yellow solid.

MS (DCI/NH_3) m/z 355 (100%) ($M+NH_4$);

^{1}H NMR (300 MHz, DMSO-d_6) δ 3.37 (s, 3H), 4.68 (s, 1H), 4.97 (q, 4H), 7.29 (d, 1H), 7.50 (s, 1H), 7.52 (d, 1H), 10.70 (s, 1H);

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 58.54; H, 3.68; N, 8.53. Found: C, 58.20; H, 3.72; N, 8.47.

Example 61

9-(3,4-dibromophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 23.5 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the

corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 3,4-dibromobenzaldehyde.

MS (ESI(+)) m/z 440 $(M+H)^+$;

MS (ESI(-)) m/z 438 $(M-H)^-$;

^1H NMR (300 MHz, DMSO-d_6) δ 1.87-1.96 (m, 2H), 2.22-2.28 (m, 2H), 2,55-2.60 (m, 2H), 4.64 (s, 1H), 4.90 (q, 2H), 7.13 (d, 1H), 7.52 (s, 1H), 7.62 (d, 1H), 10.18 (br s, 1H); Anal. Calcd for $C_{17}H_{13}Br_2NO_3$.0.1 C_6H_{14}: C, 47.22; H, 3.24; N, 3.13. Found: C, 47.16; H, 3.39; N, 2.93.

Example 62

9-(3,4-dibromophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 32.5 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 3,4-dibromobenzaldehyde.

MS (ESI(+)) m/z 440 $(M+H)^+$;

MS (ESI(-)) m/z 438 $(M-H)^-$;

^1H NMR (300 MHz, DMSO-d_6) δ 1.87-1.96 (m, 2H), 2.22-2.28 (m, 2H), 2,55-2.60 (m, 2H), 4.64 (s, 1H), 4.90 (q, 2H), 7.13 (d, 1H), 7.52 (s, 1H), 7.62 (d, 1H), 10.18 (br s, 1H); Anal. Calcd for $C_{17}H_{13}Br_2NO_3$: C, 46.50; H, 2.98; N, 3.19. Found: C, 46.68; H, 3.13; N, 3.03.

Example 63

9-(4-methyl-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 32 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the

corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 4-methyl-3-nitrobenzaldehyde.

MS (ESI(+)) m/z 341 $(M+H)^+$;

MS (ESI(-)) m/z 339 $(M-H)^-$;

^1H NMR (300 MHz, DMSO-d_6) δ 1.86-1.97 (m, 2H), 2.22-2.29 (m, 2H), 2.44 (s, 3H), 2.55-2.62 (m, 2H), 4.75 (s, 1H), 4.90 (q, 2H), 7.37 (d, 1H), 7.48 (d, 1H), 7.73 (s, 1H), 10.20 (br s, 1H);

Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.27; H, 4.83; N, 8.01.

Example 64

9-(4-methyl-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 37 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 4-methyl-3-nitrobenzaldehyde.

MS (ESI(+)) m/z 341 $(M+H)^+$;

MS (ESI(-)) m/z 339 $(M-H)^-$;

^1H NMR (300 MHz, DMSO-d_6) δ 1.86-1.97 (m, 2H), 2.22-2.29 (m, 2H), 2.44 (s, 3H), 2.55-2.62 (m, 2H), 4.75 (s, 1H), 4.90 (q, 2H), 7.37 (d, 1H), 7.48 (d, 1H), 7.73 (s, 1H), 10.20 (br s, 1H);

Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.36; H, 4.85; N, 8.17.

Example 65

9-(3,4-dichlorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 28.5 minutes, after chiral HPLC resolution (Gilson 215-

automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 3,4-dichlorobenzaldehyde.

MS (ESI(+)) m/z 350 $(M+H)^+$;

MS (ESI(-)) m/z 348 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.87-1.96 (m, 2H), 2.24-2.29 (m, 2H), 2.55-2.61 (m, 2H), 4.68 (s, 1H), 4.88 (q, 2H), 7.18 (d, 1H), 7.37 (s, 1H), 7.49 (d, 1H), 10.19 (br s, 1H); Anal. Calcd for $C_{17}H_{13}Cl_2NO_3$: C, 58.31; H, 3.74; N, 4.00. Found: C, 58.12; H, 3.85; N, 3.89.

Example 66

9-(3,4-dichlorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 39 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 3,4-dichlorobenzaldehyde.

MS (ESI(+)) m/z 350 $(M+H)^+$;

MS (ESI(-)) m/z 348 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.87-1.96 (m, 2H), 2.24-2.29 (m, 2H), 2.55-2.61 (m, 2H), 4.68 (s, 1H), 4.88 (q, 2H), 7.18 (d, 1H), 7.37 (s, 1H), 7.49 (d, 1H), 10.19 (br s, 1H); Anal. Calcd for $C_{17}H_{13}Cl_2NO_3$: C, 58.31; H, 3.74; N, 4.00. Found: C, 58.01; H, 3.82; N, 3.87.

Example 67

9-(4-chloro-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 33 minutes, after chiral HPLC resolution (Gilson 215-

automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the corresponding racemate from Example 52.

white solid:

MS (ESI(+)) m/z 361 $(M+H)^+$;

MS (ESI(-)) m/z 359 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88-1.96 (m, 2H), 2.25-2.60 (m, 2H), 2.56-2.61 (m, 2H), 4.79 (s, 1H), 4.90 (q, 2H), 7.55 (d, 1H), 7.65 (d, 1H), 7.81 (s, 1H), 10.27 (s, 1H);

Anal. Calcd for $C_{17}H_{13}ClN_2O_5$: C, 56.60; H, 3.63; N, 7.70. Found: C, 56.36; H, 4.02; N, 7.29.

Example 68

9-(4-chloro-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 45 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the corresponding racemate from Example 52.

white solid:

MS (ESI(+)) m/z 361 $(M+H)^+$;

MS (ESI(-)) m/z 359 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88-1.96 (m, 2H), 2.25-2.60 (m, 2H), 2.56-2.61 (m, 2H), 4.79 (s, 1H), 4.90 (q, 2H), 7.55 (d, 1H), 7.65 (d, 1H), 7.81 (s, 1H), 10.27 (s, 1H);

Anal. Calcd for $C_{17}H_{13}ClN_2O_5$: C, 56.60; H, 3.63; N, 7.70. Found: C, 56.37; H, 3.90; N, 7.53.

Example 69

9-(3,4-difluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 22.5 minutes, after chiral HPLC resolution (Gilson 215-

automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 3,4-difluorobenzaldehyde.

white solid:

MS (ESI(+)) m/z 318 $(M+H)^+$;

MS (ESI(-)) m/z 316 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88-1.98 (m, 2H), 2.22-2.30 (m, 2H), 2.55-2.64 (m, 2H), 4.68 (s, 1H), 4.89 (q, 2H), 7.05 (br s, 1H), 7.17 (t, 1H), 7.28 (q, 1H), 10.16 (s, 1H);

Anal. Calcd for $C_{17}H_{13}F_2NO_3$: C, 64.35; H, 4.13; N, 4.30. Found: C, 64.20; H, 4.37; N, 3.96.

Example 70

9-(3,4-difluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 27 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10mL/minute, hexane:methyl alcohol:methylene chloride(60:26:13) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 3,4-difluorobenzaldehyde.

white solid:

MS (ESI(+)) m/z 318 $(M+H)^+$;

MS (ESI(-)) m/z 316 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88-1.98 (m, 2H), 2.22-2.30 (m, 2H), 2.55-2.64 (m, 2H), 4.68 (s, 1H), 4.89 (q, 2H), 7.05 (br s, 1H), 7.17 (t, 1H), 7.28 (q, 1H), 10.16 (s, 1H);

Anal. Calcd for $C_{17}H_{13}F_2NO_3$: C, 64.35; H, 4.13; N, 4.30. Found: C, 63.97; H, 4.22; N, 4.07.

Example 71

8-(4-methyl-3-nitrophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 30 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate = 10 mL/minute, hexane:methyl alcohol:methylene chloride(50:33:17) of the corresponding racemate prepared as described in Example 6 substituting 3-bromo-4-fluorobenzaldehyde with 4-methyl-3-nitrobenzaldehyde.

white solid:

MS (ESI(+)) m/z 327 $(M+H)^+$;

MS (ESI(-)) m/z 325 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (t, 2H), 2.46 (s, 3H), 2.62-2.74 (m, 2H), 4.67 (s, 1H), 4.98 (q, 2H), 7.40 (d, 1H), 7.50 (d, 1H), 7.78 (s, 1H), 10.67 (br s, 1H);

Anal. Calcd for $C_{17}H_{14}N_2O_5.0.4\ H_2O$: C, 61.22; H, 4.47; N, 8.40. Found: C, 61.27; H, 4.48; N, 7.94.

Example 72

8-(4-methyl-3-nitrophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 36 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10 mL/minute, hexane:methyl alcohol:methylene chloride(50:33:17) of the corresponding racemate prepared as described in Example 6 substituting 3-bromo-4-fluorobenzaldehyde with 4-methyl-3-nitrobenzaldehyde.

yellow solid:

MS (ESI(+)) m/z 327 $(M+H)^+$;

MS (ESI(-)) m/z 325 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (t, 2H), 2.46 (s, 3H), 2.62-2.74 (m, 2H), 4.67 (s, 1H), 4.98 (q, 2H), 7.40 (d, 1H), 7.50 (d, 1H), 7.78 (s, 1H), 10.67 (br s, 1H);
Anal. Calcd for $C_{17}H_{14}N_2O_5$.0.25 H_2O: C, 61.72; H, 4.42; N, 8.47. Found: C, 62.08; H, 4.66; N, 7.99.

Example 73

8-(3,4-dichlorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 23 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10 mL/minute, hexane:methyl alcohol:methylene chloride(50:33:17) of the corresponding racemate prepared as described in Example 6 substituting 3-bromo-4-fluorobenzaldehyde with 3,4-dichlorobenzaldehyde.
MS (ESI(+)) m/z 336 $(M+H)^+$;
MS (ESI(-)) m/z 334 $(M-H)^-$;
^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (t, 2H), 2.59-2.78 (m, 2H), 4.60 (s, 1H), 4.96 (q, 2H), 7.22 (d, 1H), 7.43 (s, 1H), 7.52 (d, 1H), 10.59 (s, 1H);
Anal. Calcd for $C_{16}H_{11}Cl_2NO_3$.0.1 C_6H_{14}.0.4 H_2O: C, 56.64; H, 3.78; N, 3.98. Found: C, 56.73; H, 3.58; N, 3.55.

Example 74

8-(3,4-dichlorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 30.5 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10 mL/minute, hexane:methyl alcohol:methylene chloride(50:33:17) of the corresponding racemate prepared as described in Example 6 substituting 3-bromo-4-fluorobenzaldehyde with 3,4-dichlorobenzaldehyde.

MS (ESI(+)) m/z 336 $(M+H)^+$;

MS (ESI(-)) m/z 334 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (t, 2H), 2.59-2.78 (m, 2H), 4.60 (s, 1H), 4.96 (q, 2H), 7.22 (d, 1H), 7.43 (s, 1H), 7.52 (d, 1H), 10.59 (s, 1H);

Anal. Calcd for $C_{16}H_{11}Cl_2NO_3$.0.15 C_6H_{14}.0.3 H_2O: C, 57.26; H, 3.9; N, 3.95. Found: C, 57.46; H, 3.62; N, 3.48.

Example 75

8-[4-fluoro-3-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 62.5 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10 mL/minute, hexane:methyl alcohol:methylene chloride(75:16.5:8.5) of the corresponding racemate prepared as described in Example 6 substituting 3-bromo-4-fluorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde.

MS (ESI(+)) m/z 354 $(M+H)^+$;

MS (ESI(-)) m/z 352 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (t, 2H), 2.55-2.74 (m, 2H), 4.70 (s, 1H), 4.88 (q, 2H), 7.39 (t, 1H), 7.52-7.60 (m, 2H), 10.70 (br s, 1H);

Anal. Calcd for $C_{17}H_{11}F_4NO_3$: C, 57.80; H, 3.14; N, 3.96. Found: C, 57.82; H, 3.18; N, 3.60.

Example 76

8-[4-fluoro-3-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 71 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10 mL/minute, hexane:methyl alcohol:methylene chloride(75:16.5:8.5) of the corresponding

racemate prepared as described in Example 6 substituting 3-bromo-4-fluorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde.

MS (ESI(+)) m/z 354 $(M+H)^+$;

MS (ESI(-)) m/z 352 $(M-H)^-$;

^1H NMR (300 MHz, DMSO-d_6) δ 2.29 (t, 2H), 2.55-2.74 (m, 2H), 4.70 (s, 1H), 4.88 (q, 2H), 7.39 (t, 1H), 7.52-7.60 (m, 2H), 10.70 (br s, 1H);

Anal. Calcd for $C_{17}H_{11}F_4NO_3$: C, 57.80; H, 3.14; N, 3.96. Found: C, 57.53; H, 3.06; N, 3.59.

Example 77

9-(3-bromo-4-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the less polar enantiomer, retention time = 23 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10 mL/minute, hexane:methyl alcohol:methylene chloride(60:26.5:13.5) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 3-bromo-4-methylbenzaldehyde (Reference: Pearson et al., J. Org. Chem. (1958), 23, 1412-1416).

MS (ESI(-)) m/z 373 $(M-H)^-$

^1H NMR (300 MHz, DMSO-d_6) δ 1.91 (m, 2H), 2.23 (s, 3H), 2.26 (m, 2H), 2.58 (m , 2H), 4.68 (s, 1H), 4.89 (q, 2H), 7.07 (dd, J=8.0, 1.5 Hz, 1H), 7.19 (d, J=8.0 Hz, 1H), 7.30 (d, J=1.5 Hz, 1H), 10.17 (s, 1H);

Anal. Calcd for $C_{18}H_{16}BrNO_3$: C, 57.77; H, 4.31; N, 3.74. Found: C, 57.61; H, 4.51; N, 3.80.

Example 78

9-(3-bromo-4-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The enantiomerically pure title compound was obtained as the more polar enantiomer, retention time = 28 minutes, after chiral HPLC resolution (Gilson 215-automated liquid handler/HPLC, (R,R)-Whelk-O1 column (2.1 cm x 25 cm), flow rate=10

mL/minute, hexane:methyl alcohol:methylene chloride(60:26.5:13.5) of the corresponding racemate prepared as described in Example 10 substituting 3-bromo-4-fluorobenzaldehyde with 3-bromo-4-methylbenzaldehyde.

MS (ESI(-)) m/z 373 $(M-H)^-$

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.91 (m, 2H), 2.23 (s, 3H), 2.26 (m, 2H), 2.58 (m , 2H), 4.68 (s, 1H), 4.89 (q, 2H), 7.07 (dd, J=8.0, 1.5 Hz, 1H), 7.19 (d, J=8.0 Hz, 1H), 7.30 (d, J=1.5 Hz, 1H), 10.17 (s, 1H);

Anal. Calcd for $C_{18}H_{16}BrNO_3$: C, 57.77; H, 4.31; N, 3.74. Found: C, 57.61; H, 4.51; N, 3.80.

Example 79

8-(3-chloro-4-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

3-Chloro-4-fluorobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as in Example 5 to provide the title compound as a white solid.

MS (DCI/NH_3) m/z 339 (100%) $(M+NH_4)$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 4.68 (s, 1H), 4.98 (q, 4H), 7.28 (m, 2H), 7.33 (d, 1H), 10.70 (s, 1H);

Anal. Calcd for $C_{15}H_9NFClO_4$: C, 56.01; H, 2.82; N, 4.35. Found: C, 55.99; H, 2.77; N, 4.19.

Example 80

8-(3,4-dibromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

3,4-Dibromobenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as in Example 5 to provide the title compound as a white solid.

MS (DCI/NH_3) m/z 445 (100%) $(M+NH_4)$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 4.64 (s, 1H), 4.98 (q, 4H), 7.21 (d, 1H), 7.61 (s, 1H), 7.68 (d, 1H), 10.72 (s, 1H);

Anal. Calcd for $C_{15}H_9NBr_2O_4.0.25C_3H_6O$: C, 42.84; H, 2.40; N, 3.17. Found: C, 42.82; H, 2.24; N, 3.07.

Example 81

8-(3-bromo-4-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

3-Bromo-4-methylbenzaldehyde (Reference: Pearson et al., J. Org. Chem. (1958), 23, 1412-1416) was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 5 to provide the title compound.

MS (ESI(-)) m/z 361.01 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 4.60 (s, 1H), 4.88 - 5.05 (m, 4H), 7.17 (dd, J=7.7, 1.8 Hz, 1H), 7.28 (d, J=7.7 Hz, 1H), 7.42 (d, J=1.8 Hz, 1H), 10.68 (s, 1H);

Anal. Calcd for $C_{16}H_{12}BrNO_4$: C, 53.06; H, 3.34; N, 3.87. Found: C, 52.77; H, 3.44; N, 3.68.

Example 82

8-[4-chloro-3-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

4-Chloro-3-trifluoromethylbenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as in Example 5 to provide the title compound as a white solid.

MS (DCI/NH_3) m/z 389 (100%) $(M+NH_4)$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 4.82 (s, 1H), 4.99 (q, 4H), 7.59 (d, 1H), 7.66 (d, 1H), 7.74 (s, 1H), 10.78 (s, 1H);

Anal. Calcd for $C_{16}H_9ClFNO_4$: C, 51.70; H, 2.44; N, 3.77. Found: C, 50.86; H, 2.22; N, 3.59.

Example 83

8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,4-e]pyridine-1,7(3H)-dione

Example 83A

methyl 4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxylate

A mixture of pyrrolidine-2,4-dione (Reference: G. Lowe, H. W. Yeung, J. Chem. Soc. Perkin Trans. I, (1973), 2907-2910) (2 mmol, 198 mg), 3-bromo-4-fluorobenzaldehyde (2 mmol, 406 mg) and methyl 3-aminocrotonate (2 mmol) in ethyl alcohol (7 mL) was heated in a sealed tube at 80 °C for a period of 48 hours. The reaction mixture was concentrated, and the residue was flash chromatographed (silica gel, methylene chloride:ethyl acetate:methyl alcohol, 4:2:0.5) to provide the title compound as a yellow solid (165 mg, 22% yield).

Example 83B

8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,4-e]pyridine-1,7(3H)-dione

A suspension of the product from Example 83A (0.42 mmol, 159 mg) in chloroform (4 mL) was treated at 0 °C with pyridine (1.2 equiv, 0.04 mL) and pyridinium tribromide (1.1 equiv, 147 mg). The reaction mixture was allowed to warm up to ambient temperature over a period of 1 hour, and stirred at that temperature for another one hour. The homogeneous solution was poured into a dilute aqueous hydrochloric acid solution, and the layers were separated. The organic phase was dried over magnesium sulfate, filtered and concentrated. The solid residue was dissolved in chloroform (2 mL), and heated at 75 °C overnight. Following concentration, flash chromatography (silica gel, methylene chloride:ethyl acetate:methyl alcohol, 4:2:0.7 to 4:2:1.7) of the residue provided the title compound (42 mg, 28% yield).

MS (APCI+) m/z 365 $(M+H)^+$;

^{1}H NMR (DMSO-d_6) δ 4.00 (ABq, 2H), 4.61 (s, 1H), 4.91 (ABq, 2H), 7.24-7.30 (m, 2H), 7.50 (d, 1H), 7.58 (s, 1H);

Anal. Calcd for $C_{15}H_{10}N_2O_3FBr \cdot 1.0\ H_2O$: C, 47.02; H, 3.16; N, 7.31. Found: C, 47.00; H, 2.81; N, 7.07.

Example 84

2-(2-aminoethyl)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

Ethylenediamine was substituted for methylamine and processed as described in Example 8C to provide the title compound as a yellow solid.

MS (APCI+) m/z 420 $(M+H)^+$;

^1H NMR (DMSO-d_6) δ 1.82-1.97 (m, 2H), 2.19-2.29 (m, 2H), 2.47-2.65 (m, 2H), 2.60 (t, 2H), 3.07-3.20 (m, 2H), 4.08 (ABq, 2H), 4.71 (s, 1H), 7.16-7.23 (m, 2H), 7.40-7.45 (m, 1H);

Anal. Calcd for $C_{19}H_{19}N_3O_2FBr \cdot 1.0\ H_2O$: C, 52.07; H, 4.83; N, 9.59. Found: C, 51.61; H, 5.01; N, 11.36.

Example 85

8-(4-bromo-3-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

Example 85a

4-bromo-3-methylbenzaldehyde

A solution of 2,5-dibromotoluene (5.00g, 2.75 mL, 20.0 mmol) in diethyl ether (50 mL) was stirred under nitrogen at -78 °C. N-Butyllithium (10 mL, 2.0 M, 20.0 mmol) was added dropwise over 10 minutes and stirring continued for a further 1 hour. Anhydrous N,N-dimethylformamide (2.19 g, 2.32 mL, 30.0 mmol) was added dropwise over 15 minutes and the solution allowed to reach -40 °C over 4 hours. The reaction mixture was quenched by the addition of aqueous saturated sodium bicarbonate. The solvent was removed in vacuo, and the residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic phase was washed with water (2 x 50 mL), brine, dried over sodium sulfate, filtered and concentrated to give a colorless oil (55% yield) as a 7:3 mixture of 4-bromo-3-methylbenzaldehyde to 4-bromo-2-methylbenzaldehyde.

Example 85b

8-(4-bromo-3-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

4-Bromo-3-methylbenzaldehyde (1.43 equivalents) was processed as described in Example 5 to provide the title compound as a white solid.

MS (DCI/NH_3) m/z 381 (100%) ($M+NH_4$);

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 4.58 (s, 1H), 4.97 (q, 4H), 7.01 (d, 1H), 7.22 (s, 1H), 7.48 (d, 1H), 10.70 (s, 1H);

Anal. Calcd for $C_{16}H_{12}BrNO_4$: C, 53.06; H, 3.34; N, 3.87. Found: C, 52.67; H, 3.23; N, 3.60.

Example 86

8-(4-fluoro-3-isopropenylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

Example 86a

tributyl(isopropenyl)stannane

Tributyltin chloride (5.00g, 4.17 mL, 15.3 mmol) was dissolved in dry tetrahydrofuran (30 mL) and isopropenylmagnesium bromide (30.7 mL, 0.5 M, 15.3 mmol) in hexane was added dropwise over 10 minutes. The solution was warmed to 50 °C, allowed to cool to ambient temperature, and stirred for 18 hours. The solution was poured into hexane (200 mL), filtered, and the filtrate was concentrated in vacuo to yield a colorless oil (4.44g, 87% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 15H), 1.30 (m, 6H), 1.48 (m, 6H), 4.58 (s, 1H), 1.96 (s, 3H), 5.04 (s, 1H), 5.68 (s, 1H).

Example 86b

8-(4-fluoro-3-isopropenylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

The product from Example 5 was processed as described in Example 91 substituting tributyl(2-furyl)stannane with the product from Example 86A to provide the title compound as a white solid.

MS (DCI/NH_3) m/z 345 (100%) ($M+NH_4$);

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.07 (s, 3H), 4.63 (s, 1H), 4.97 (q, 4H), 5.20 (s, 1H), 5.25 (s, 1H), 7.16 (m, 2H), 7.24 (d, 1H), 10.70 (s, 1H);

Anal. Calcd for $C_{18}H_{14}FNO_4$.0.25 H_2O: C, 65.16; H, 4.40; N, 4.22. Found: C, 65.40; H, 4.17; N, 3.89.

Example 87

(9S)-2-(2-aminoethyl)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione

The product from Example 18C was treated with ethylenediamine and processed as described in Example 8C to provide the title compound as a yellow powder.

MS (ESI(+)) m/z 420 $(M+H)^+$;

MS (ESI(-)) m/z 418 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85-1.97 (m, 2H), 2.15-2.30 (m, 4H), 2.52-2.58 (m, 2H), 3.18-3.30 (m, 2H), 4.07 (m, 2H), 7.18 (m, 2H), 7.41 (d, 1H), 9.79 (s, 1H);

Anal. Calcd for $C_{19}H_{19}BrFN_3O_2$.0.4 C_6H_{14}: C, 56.52; H, 5.05; N, 9.24. Found: C, 56.79; H, 5.06; N, 9.00.

Example 88

8-(3-iodo-4-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

Example 88a

3-Iodo-4-methylbenzaldehyde

To a slurry of 3-iodo-4-methylbenzoic acid (5.0 g, 19.1 mmol) in 100 mL of dry tetrahydrofuran was added borane-methyl sulfide complex (2.3 mL, 22.9 mmol). This mixture was refluxed for 60 minutes and then cooled to room temperature. After concentration a dark brown oil was obtained. This oil was dissolved in 32 mL of methylene chloride and the solution was treated with pyridinium chlorochromate (4.55 g, 21 mmol). This mixture was refluxed for 60 minutes, cooled to ambient temperature, and concentrated. The dark red oil obtained was diluted with ethyl acetate and washed succesively with water, 1 N aqueous hydrochloric acid, aqueous saturated sodium bicarbonate, and brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel using hexane-ethyl acetate (20:1) as eluent to yield the title aldehyde as a pale yellow solid (1.7g, 36% yield).

Example 88b

8-(3-iodo-4-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

3-Iodo-4-methylbenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 5 to provide the title compound as a white solid. MS (ESI(-)) m/z 408 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3H), 4.57 (s, 1H), 4.98 (q, J=12.54 Hz, 4H), 7.19 (dd, J=8.07, 1.11 Hz, 1H), 7.26 (d, J=8.07 Hz, 1H), 7.66 (d, J=1.11 Hz, 1H);

Anal. Calcd for $C_{16}H_{12}INO_4$: C, 46.97; H, 2.96; N, 3.42. Found: C, 46.65; H, 2.80; N, 3.26.

Example 89

(-) 9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

Example 89A

methyl 4-(3-bromo-4-fluorophenyl)-2,6,6-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate

A stirred solution of 3-bromo-4-fluorobenzaldehyde (1.80 g, 8.87 mmol), 4,4-dimethyl-1,3-cyclohexanedione (1.24 g, 8.87 mmol), and methyl 3-aminocrotonate (1.02 g mg, 8.87 mmol) in methanol (50 mL) was treated with anhydrous ammonium acetate (957 mg, 12.4 mmol) and the mixture was heated at reflux for 36 hours. The reaction mixture was cooled to ambient temperature and the white solid that precipitated was isolated by filtration. The solid was triturated sequentially with cold methanol followed by diethyl ether to provide the title compound as a white solid: 1.54 g (3.64 mmol, 41%).

Enantiomers were resolved by chiral HPLC using a (R,R)-Whelk-O 1 column (2.1 cm x 25 cm), 25% EtOH/hexanes, flow rate=10 mL/min.

Less polar isomer, retention time=29 minutes:

MS (DCI/NH_3) m/z 422 $(M+H)^+$;

^1H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 3H), 1.02 (s, 3H), 1.64-1.78 (m, 2H), 2.31 (s, 3H), 3.31-3.39 (m, 2H), 3.57 (s, 3H), 4.86 (s, 1H), 7.12-7.23 (m, 2H), 7.36 (dd, J=6.6, 2.1 Hz, 1H), 9.20 (br s, 1H);

Anal. Calcd for $C_{20}H_{21}BrFNO_3$: C, 56.88; H, 5.01; N, 3.32. Found: C, 56.69; H, 5.16; N, 3.34.

More polar isomer, retention time=36 minutes:

MS (DCI/NH_3) m/z 422 $(M+H)^+$;

^1H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 3H), 1.02 (s, 3H), 1.64-1.78 (m, 2H), 2.31 (s, 3H), 3.31-3.39 (m, 2H), 3.57 (s, 3H), 4.86 (s, 1H), 7.12-7.23 (m, 2H), 7.36 (dd, J=6.6, 2.1 Hz, 1H), 9.20 (br s, 1H);

Anal. Calcd for $C_{20}H_{21}BrFNO_3$: C, 56.88; H, 5.01; N, 3.32. Found: C, 56.74; H, 5.07; N, 3.40.

Example 89B

(-) 9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The more polar enantiomer (272 mg, 0.644 mmol) from Example 89A was dissolved in chloroform (6 mL) and N-bromosuccinimide (115 mg, 0.644 mmol) was added at 23 °C. After 3 hours of stirring at 23 °C, the reaction mixture was partitioned between ethyl acetate (20 mL) and water (8 mL). The organic portion was washed with brine (5 mL) and then dried (sodium sulfate), filtered, and concentrated to give an off-yellow solid. The crude solid was placed in a 25 mL round bottom flask and immersed in a pre-heated (130 °C) oil bath under a stream of nitrogen for 1.5 hours. The resulting residue was dissolved in a minimum volume of methylene chloride and purified by flash chromatography (silica, elution with 10% ethyl acetate/methylene chloride) to provide the title compound as an off-white solid (194 mg, 0.478 mmol, 74%).

$[\alpha]_D^{23}$ -109° (c 0.3, $CHCl_3$);

mp 197-198 °C;

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (s, 3H), 0.94 (s, 3H), 1.75 (t, J=6.3 Hz, 2H), 2.48-2.69 (m, 2H), 4.61 (s, 1H), 4.83 (ABq, J_{AB}=16.5 Hz, $\Delta\nu_{AB}$=29.7 Hz, 2H), 7.13-7.24 (m, 2H), 7.38 (dd, J=6.7, 2.0 Hz, 1H), 10.11 (br s, 1H);

^{13}C NMR (DMSO-d_6) δ 23.6, 24.1, 24.8, 33.7, 33.9, 65.2, 101.3, 107.2, 109.0, 116.1, 128.5, 132.0, 143.4, 151.2, 156.3, 171.3, 199.5;

MS (DCI/NH_3) m/z 423 $(M+NH_4)^+$;

Anal. Calcd for $C_{19}H_{17}BrFNO_3$: C, 56.17; H, 4.22; N, 3.45. Found: C, 56.09; H, 4.16; N, 3.44.

Example 90

(+) 9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione

The less polar isomer from Example 89A was subjected to the bromination/lactonization procedure described in Example 89B to provide the title compound.

$[\alpha]_D^{23}$ +114° (c 0.3, $CHCl_3$);

mp 197-198 °C;

MS (DCI/NH_3) m/z 423 $(M+NH_4)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (s, 3H), 0.94 (s, 3H), 1.75 (t, J=6.3 Hz, 2H), 2.48-2.69 (m, 2H), 4.61 (s, 1H), 4.83 (ABq, J_{AB}=16.5 Hz, $\Delta\nu_{AB}$=29.7 Hz, 2H), 7.13-7.24 (m, 2H), 7.38 (dd, J=6.7, 2.0 Hz, 1H), 10.11 (br s, 1H);

^{13}C NMR (DMSO-d_6) δ 23.6, 24.1, 24.8, 33.7, 33.9, 65.2, 101.3, 107.2, 109.0, 116.1, 128.5, 132.0, 143.4, 151.2, 156.3, 171.3, 199.5;

Anal. Calcd for $C_{19}H_{17}BrFNO_3$: C, 56.17; H, 4.22; N, 3.45. Found: C, 56.10; H, 4.26; N, 3.51.

Example 91

8-[3-(2-furyl)-4-methylphenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione

To a slurry of the product from Example 81 (130 mg, 0.36 mmol) in 5 mL of N,N-dimethylformamide was added tributyl(2-furyl)stannane (0.14 mL, 0.43 mmol), di-tert-butyl dicarbonate (75 mg, 0.36 mmol) and tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.04 mmol). The reaction mixture was heated at 120 °C in a sealed high pressure tube overnight. Then it was cooled to ambient temperature and diluted with ethyl acetate. The solution was washed succesively with brine, 1N hydrochloric acid, aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel using methylene chloride-methyl alcohol (20:1) as eluent to yield the title compound as a pale yellow solid. The title compound was recrystallized from methylene chloride-methyl alcohol-diethyl ether (1:1:20) (62mg, 49%).

MS (ESI(-)) m/z 348 $(M-H)^-$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (s, 3H), 4.62 (s, 1H), 4.98 (q, J=12.54 Hz, 4H), 6.63 (q, J=1.04 Hz, 1H), 6.70 (d, J=3.31 Hz, 1H), 7.10 (dd, J=7.72, 1.84 Hz, 1H), 7.22 (d, J=8.09 Hz, 1H), 7.53 (d, J=1.84 Hz, 1H), 7.79 (d, J=1.11 Hz, 1H);

Anal. Calcd for $C_{20}H_{15}NO_5$.0.2 H_2O: C, 68.76; H, 4.33; N, 4.01. Found: C, 67.82; H, 4.23; N, 3.63.

Example 92

9-(3-bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydrocyclopenta[b]pyrano[3,4-e]pyridine-1,8-dione

Example 92A

4-(1-ethoxyethoxy)-1-butyne

3-Butyn-1-ol (46.33 g, 0.661 mole) was dissolved in methylene chloride (700 mL) and treated with ethyl vinyl ether (0.661 mole, 63.2 mL) and pyridinium p-toluenesulfonate (0.033, 8.31 g) (note: upon addition of pyridinium p-toluenesulfonate an exothermic reaction takes place). After stirring for a period of 2 hours, the reaction mixture was concentrated and filtered through a pad of silica gel (ethyl acetate:hexane, 1:1) to provide the title compound as a colorless liquid (80.29 g, 85.5% yield).

Example 92B

benzyl 5-(1-ethoxyethoxy)-2-pentynoate

A solution of the product from Example 92A (79.99 g, 0.563 mole) in tetrahydrofuran (1 L) was treated dropwise at -78 °C with n-butyllithium (2.5 M in hexane, 0.563 mole, 225 mL). The reaction mixture was stirred at -78 °C for half an hour and then benzyl chloroformate (0.563 mole, 80.4 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 2 hours, allowed to warm to ambient temperature and stirred overnight. After quenching with water, ethyl acetate was added and the layers were separated. The organic layer was dried over magnesium sulfate, filtered and concentrated. Flash chromatography of the residue (silica, hexane to hexane:ethyl acetate, 30:1 to 4:1) provided the title compound as a colorless oil (155.5 g, 78% yield).

Example 92C

benzyl 5-hydroxy-2-pentynoate

A solution of the product from Example 92B (122.1 g, 0.442 mole) in acetone (400 mL) was treated at ambient temperature with an aqueous hydrochloric acid solution (0.5 N, 200 mL). The reaction mixture was stirred for 6 hours and then diluted with water and ethyl acetate. The layers were separated, and the organic layer was dried over magnesium sulfate, filtered and concentrated to provide the title compound as a colorless oil (90.17 g, 100% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (t, 2H), 3.79 (t, 2H), 5.19 (s, 2H), 7.32-7.40 (m, 5H).

Example 92D

4-(benzyloxy)-5,6-dihydro-2H-pyran-2-one

A heterogeneous mixture of benzyl alcohol (2.65 mole, 274.4 mL), mercury(II) oxide (red) (13.26 mmol, 2.87 g) and boron trifluoride diethyl etherate (0.133 mole, 16.3 mL) was heated at 60 °C for 3 hours (eventually turned homogeneous). Then a solution of the product from Example 92C (90.17 g, 0.442 mole) in benzyl alcohol (91.5 mL) was added at ambient temperature, and the reaction mixture was stirred at 70 °C for 4 hours and again at ambient temperature overnight. It was poured into an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated. Flash chromatography (silica, hexane to hexane:ethyl acetate, 30:1 to 1:2) provided the title compound as a white solid (49.6 g, 55% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (t, 2H), 4.38 (t, 2H), 4.95 (s, 2H), 5.28 (s, 1H), 7.32-7.46 (m, 5H).

Example 92E

dihydro-2H-pyran-2,4(3H)-dione

The product from Example 92D (9.17 g, 0.045 mole) was dissolved in isopropanol (500 mL) and treated with palladium hydroxide (20 wt. % palladium, dry basis, on carbon) (4 g) under nitrogen atmosphere. The reaction mixture was stirred under hydrogen

atmosphere at atmospheric pressure overnight. It was filtered through a pad of silica gel (elution with ethyl acetate). The filtrate was concentrated to provide the title compound as a white solid (4.28 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (t, 2H), 3.57 (s, 2H), 4.61 (t, 2H).

Example 92F

9-(3-bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydrocyclopenta[b]pyrano[3,4-e]pyridine-1,8-dione

A mixture of the product from Example 92E (1.5 mmol, 171 mg), 3-bromo-4-fluorobenzaldehyde (1.5 mmol, 305 mg) and 3-amino-2-cyclopenten-1-one (1.5 mmol, 146 mg) was suspended in ethyl alcohol (5 mL). The reaction mixture was heated in a sealed tube at 80 °C over a period of 72 hours. The precipitate formed was collected by filtration and dried to provide the title compound (246 mg, 43% yield).

MS (APCI+) m/z 378 $(M+H)^+$;

^{1}H NMR (DMSO-d_6) δ 2.28 (t, 2H), 2.52-2.86 (m, 4H), 4.20-4.38 (m, 2H), 4.63 (s, 1H), 7.20-7.27 (m, 2H), 7.45 (d, 1H), 10.27 (bs, 1H);

Anal. Calcd for $C_{17}H_{13}NO_3FBr$: C, 53.99; H, 3.46; N, 3.70. Found: C, 53.38; H, 3.76; N, 3.49.

Example 93

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-1H-pyrano[4,3-b]quinoline-1,9(5H)-dione

A mixture of the product from Example 92E (1.5 mmol, 171 mg), 3-bromo-4-fluorobenzaldehyde (1.5 mmol, 305 mg) and 3-amino-2-cyclohexen-1-one (1.5 mmol, 167 mg) was suspended in ethyl alcohol (5 mL). The reaction mixture was heated in a sealed tube at 80 °C over a period of 72 hours. The precipitate formed was collected by filtration and dried to provide the title compound (265 mg, 45% yield).

MS (APCI-) m/z 390 $(M-H)^-$;

^{1}H NMR (DMSO-d_6) δ 1.73-2.00 (m, 2H), 2.19-2.29 (m, 2H), 2.54-2.80 (m, 4H), 4.10-4.35 (m, 2H), 4.80 (s, 1H), 7.18-7.23 (m, 2H), 7.39 (dd, 1H), 9.72 (bs, 1H);

Anal. Calcd for $C_{18}H_{15}NO_3FBr$: C, 55.12; H, 3.85; N, 3.57. Found: C, 55.00; H, 3.79; N, 3.54.

Example 94

10-[4-fluoro-3-(trifluoromethyl)phenyl]-3,4,6,7,8,10-hexahydro-1H-pyrano[4,3-b]quinoline-1,9(5H)-dione

4-Fluoro-3-trifluoromethylbenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 93 to provide the title compound.

MS (APCI+) m/z 382 $(M+H)^+$;

^1H NMR (DMSO-d_6) δ 1.74-2.00 (m, 2H), 2.19-2.29 (m, 2H), 2.54-2.80 (m, 4H), 4.12-4.35 (m, 2H), 4.87 (s, 1H), 7.35 (dd, 1H), 7.47-7.56 (m, 2H), 9.77 (bs, 1H);

Anal. Calcd for $C_{19}H_{15}NO_3F_4$: C, 59.85; H, 3.96; N, 3.67. Found: C, 59.66; H, 3.88; N, 3.60.

Example 95

9-[4-fluoro-3-(trifluoromethyl)phenyl]-3,4,5,6,7,9-hexahydrocyclopenta[b]pyrano[3,4-e]pyridine-1,8-dione

4-Fluoro-3-trifluoromethylbenzaldehyde was substituted for 3-bromo-4-fluorobenzaldehyde and processed as described in Example 92 to provide the title compound.

MS (APCI+) m/z 368 $(M+H)^+$;

^1H NMR (DMSO-d_6) δ 2.28 (t, 2H), 2.52-2.86 (m, 4H), 4.21-4.38 (m, 2H), 4.72 (s, 1H), 7.38 (dd, 1H), 7.50-7.59 (m, 2H), 10.31 (bs, 1H);

Anal. Calcd for $C_{18}H_{13}NO_3F_4$: C, 58.86; H, 3.57; N, 3.81. Found: C, 58.55; H, 3.82; N, 3.63.

Determination of Potassium Channel Opening Activity
Membrane Hyperpolarization Assays

Compounds were evaluated for potassium channel opening activity using primary cultured guinea-pig urinary bladder (GPB) cells.

For the preparation of urinary bladder smooth muscle cells, urinary bladders were removed from male guinea-pigs (Hartley, Charles River, Wilmington, MA) weighing 300-400 grams (g) and placed in ice-cold Ca^{2+}-free Krebs solution (Composition, millimolar (mM): KCl, 2.7; KH_2PO_4, 1.5; NaCl, 75; Na_2HPO_4, 9.6; $Na_2HPO_4.7H_2O$, 8; $MgSO_4$, 2; glucose, 5; HEPES, 10; pH 7.4). Cells were isolated by enzymatic dissociation (Klockner, U. and Isenberg, G., Pflugers Arch. (1985), 405, 329-339). The bladder was cut into small sections and incubated in 5 milliliters (mL) of the Kreb's solution containing 1 milligram per milliliter (mg/mL) of collagenase (Sigma, St. Louis, MO) and 0.2 mg/mL of pronase (Calbiochem, La Jolla, CA) with continuous stirring in a cell incubator for 30 minutes. The mixture was then centrifuged at 1300 x g for 5 minutes, and the pellet resuspended in Dulbecco's phosphate buffered saline (PBS) (GIBCO, Gaithersburg, MD) and recentrifuged to remove residual enzyme. The cell pellet was resuspended in 5 mL growth media (composition: Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 100 units/mL penicillin, 100 units/mL streptomycin and 0.25 mg/mL amphotericin B) and further dissociated by pipetting the suspension through a flame-polished Pasteur pipette and passing it through a polypropylene mesh membrane (Spectrum, Houston, TX). The cell density was adjusted to 100,000 cells/mL by resuspension in growth media. Cells were plated in clear-bottomed black 96-well plates (Packard) for membrane potential studies at a density of 20,000 cells/well and maintained in a cell incubator with 90% air:10% CO_2 until confluent. Cells were confirmed to be of smooth muscle type by cytoskeletal staining using a monoclonal mouse anti human-α-smooth muscle actin (Biomeda, Foster City, CA).

Functional activity at potassium channels was measured by evaluating changes in membrane potential using the bis-oxonol dye $DiBAC(4)_3$ (Molecular Probes) in a 96-well cell-based kinetic assay system using a Fluorescent Imaging Plate Reader (FLIPR) (K.S. Schroeder et al., J. Biomed. Screen., v. 1 pp. 75-81 (1996)). $DiBAC(4)_3$ is an anionic

potentiometric probe which partitions between cells and extracellular solution in a membrane potential-dependent manner. With increasing membrane potential (for example, K^+ depolarization), the probe further partitions into the cell; this is measured as an increase in fluorescence due to dye interaction with intracellular lipids and proteins. Conversely, decreasing membrane potential (hyperpolarization by potassium channel openers) evokes a decrease in fluorescence.

Confluent guinea-pig urinary bladder cells cultured in black clear-bottomed 96-well plates were rinsed twice with 200 mL assay buffer (composition, mM: HEPES, 20; NaCl, 120; KCl, 2; $CaCl_2$, 2; $MgCl_2$, 1; glucose, 5; pH 7.4 at 25 °C) containing 5 μM $DiBAC(4)_3$ and incubated with 180 mL of the buffer in a cell incubator for 30 minutes at 37 °C to ensure dye distribution across the membrane. After recording the baseline fluorescence for 5 minutes, the reference or test compounds, prepared at 10 times the concentration in the assay buffer, were added directly to the wells. Changes in fluorescence were monitored for an additional 25 minutes. Hyperpolarization responses were corrected for any background noise and were normalized to the response observed with 10 μM of the reference compound P1075 (assigned as 100%), a potent opener of smooth muscle K_{ATP} channels (Quast et al., Mol. Pharmacol., v. 43 pp. 474-481 (1993)).

Routinely, five concentrations of P1075 or test compounds (log or half-log dilutions) were evaluated and the maximal steady-state hyperpolarization values (expressed as % relative to P1075) plotted as a function of concentration. The EC_{50} (concentration that elicites 50% of the maximal response for the test sample) values were calculated by non-linear regression analysis using a four parameter sigmoidal equation. The maximal micromolar EC_{50} response of each compound (expressed as % relative to P1075) is reported. Stock solutions of compounds were prepared in 100% DMSO and further dilutions were carried out in the assay buffer and added to a 96-well plate.

Table 1

Membrane Hyperpolarization (MHP) in Guinea-Pig Bladder (GPB) Cells

Example Number	Maximal Response (% P1075)	$EC_{50}(\mu M)$
1	90.4	2.8
2	104	1.0
3	110	0.037
4	85	2.2
5	107	0.063
6	101	0.031
7	83	1.9
8	82	0.29
9	47	8.3
10	89	0.027
11	79	0.23
12	30	21
14	29	32
15	92	0.14
16	97	0.40
17	102	0.21
18	108	0.006
19	108	0.24
20	70	2.1
21	90	2.6
22	92	0.43
23	87	0.18
24	83	0.70
25	108	0.007

26	34	14
27	86	1.2
28	103	0.096
29	97	0.12
30	29	35
31	66	2.4
32	94	0.012
35	81	0.54
36	64	0.54
37	100	1.0
38	85	0.15
39	82	1.9
44	104	0.45
49	91	1.9
51	97	0.085
52	115	0.19
53	87	0.63
54	112	0.19
55	103	0.12
56	100	0.24
57	104	0.011
58	102	0.36
59	98	0.55
60	108	0.094
61	80	0.015
62	94	0.51
63	88	0.092
64	61	5.5
65	80	0.028

66	79	0.18
67	95	0.016
68	90	1.3
69	67	0.16
70	45	3.0
71	96	0.097
72	90	1.5
73	100	0.013
74	105	0.28
75	103	0.028
76	98	0.67
77	88	0.012
78	90	0.26
79	122	0.32
80	115	0.26
81	98	0.39
82	109	0.33
83	97	0.23
85	104	1.5
86	102	0.93
87	37	15
88	93	0.031
89	82	0.11

In vitro Functional models

Compounds were evaluated for functional potassium channel opening activity using tissue strips obtained from Landrace pig bladders.

Landrace pig bladders were obtained from female Landrace pigs of 9-30 kg. Landrace pigs were euthanized with an intraperitoneal injection of pentobarbital solution, Somlethal® , J.A. Webster Inc., Sterling MA. The entire bladder was removed and

immediately placed into Krebs Ringer bicarbonate solution (composition, mM: NaCl, 120; $NaHCO_3$, 20; dextrose, 11; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.5; KH_2PO_4, 1.2; K_2EDTA, 0.01, equilibrated with 5% CO_2/95% O_2 pH 7.4 at 37 °C). Propranolol (0.004 mM) was included in all of the assays to block β-adrenoceptors. The trigonal and dome portions were discarded. Strips 3-5 millimeters (mm) wide and 20 mm long were prepared from the remaining tissue cut in a circular fashion. The mucosal layer was removed. One end was fixed to a stationary glass rod and the other to a Grass FT03 transducer at a basal preload of 1.0 g. Two parallel platinum electrodes were included in the stationary glass rod to provide field stimulation of 0.05 Hz, 0.5 milli-seconds at 20 volts. This low frequency stimulation produced a stable twitch response of 100-500 centigrams. Tissues were allowed to equilibrate for at least 60 minutes and primed with 80 mM KCl. A control concentration response curve (cumulative) was generated for each tissue using the potassium channel opener P1075 as the control agonist. P1075 completely eliminated the stimulated twitch in a dose dependent fashion over a concentration range of 10^{-9} to 10^{-5} M using 1/2 log increments. After a 60 minute rinsing period, a concentration response curve (cumulative) was generated for the test agonist in the same fashion as that used for the control agonist P1075. The maximal efficacy of each compounds (expressed as % relative to P1075) is reported. The amount of agent necessary to cause 50% of the agent's maximal response (ED_{50}) was calculated using "ALLFIT" (DeLean et al., Am. J. Physiol., 235, E97 (1980)), and agonist potencies were expressed as p_{D2} (the negative logarithm). Agonist potencies were also expressed as an index relative to P1075. The index was calculated by dividing the ED_{50} for P1075 by the ED_{50} for the test agonist in a given tissue. Each tissue was used for only one test agonist, and the indices obtained from each tissue were averaged to provide an average index of potency. These data are shown in Table 2.

Table 2

Functional Potassium Channel Opening Activity in Isolated Bladder Strips

	Landrace Pig Bladder		
Example Number	Efficacy (%P1075)	pD_2	Index
2	100	5.7	0.016
3	100	6.8	0.36
5	100	6.8	0.55
15	91.5	5.9	0.13
16	99.4	6.0	0.12
17	97.5	5.8	0.068
18	81	6.9	1.6
19	100	6.3	0.14
20	91.3	5.2	0.014
21	98	5.3	0.087
23	98.3	4.8	0.021
28	94.5	6.2	0.18
29	97.5	6.7	0.46
32	95	6.6	0.40
35	71.5	6.0	0.07
38	100	6.2	0.20
39	94.8	5.6	0.053
53	98	6.4	0.18
54	94.8	6.6	0.67
55	98	6.7	0.14
56	76	5.3	0.035
58	86.2	5.6	0.038
59	92.5	5.3	0.015
60	84.5	5.7	0.08

61	99.5	7.3	0.56
62	84.8	5.5	0.04
65	91	7.1	2.4
66	94	6.4	0.37
73	58.3	6.3	1.3
74	81.8	5.4	0.046
78	82.2	5.5	0.036
79	100	5.8	0.084
81	95.8	5.4	0.059
82	88.5	5.7	0.049
86	95.3	5.4	0.018
88	100	6.2	0.17

As shown by the data in Tables 1 and 2, the compounds of this invention reduce stimulated contractions of the bladder by opening potassium channels and therefore may have utility in the treatment of diseases prevented by or ameliorated with potassium channel openers.

The term "pharmaceutically acceptable carrier," as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and

perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The present invention provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

Further included within the scope of the present invention are pharmaceutical compositions comprising one or more of the compounds of formula I-VI prepared and formulated in combination with one or more non-toxic pharmaceutically acceptable compositions. The pharmaceutical compositions can be formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), bucally or as an oral or nasal spray. The term "parenterally," as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative agents, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by various antibacterial and antifungal agents, for

example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Suspensions, in addition to the active compounds, may contain suspending agents, as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, and mixtures thereof.

If desired, and for more effective distribution, the compounds of the present invention can be incorporated into slow-release or targeted-delivery systems such as polymer matrices, liposomes, and microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter or by incorporation of sterilizing agents in the form of sterile solid compositions, which may be dissolved in sterile water or some other sterile injectable medium immediately before use.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may

also comprise buffering agents. They may optionally contain opacifying agents and can also be of such composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Injectable depot forms are made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic, parenterally acceptable diluent or solvent such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin,

polyvinylpyrrolidinone, sucrose, and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; e) solution retarding agents such as paraffin); f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate;) absorbents such as kaolin and bentonite clay; and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and

mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Compounds of the present invention may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes may be used. The present compositions in liposome form may contain, in addition to the compounds of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids

are the natural and synthetic phospholipids and phosphatidylcholines (lecithins) used separately or together.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y., (1976), p 33 et seq.

The term "pharmaceutically acceptable cation," as used herein, refers to a positively-charged inorganic or organic ion that is generally considered suitable for human consumption. Examples of pharmaceutically acceptable cations are hydrogen, alkali metal (lithium, sodium and potassium), magnesium, calcium, ferrous, ferric, ammonium, alkylammonium, dialkylammonium, trialkylammonium, tetraalkylammonium, diethanolammmonium, and choline. Cations may be interchanged by methods known in the art, such as ion exchange.

The terms "pharmaceutically acceptable salts, esters and amides," as used herein, refer to carboxylate salts, amino acid addition salts, zwitterions, esters and amides of compounds of formula I-VI which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

The term "pharmaceutically acceptable salt," as used herein, refers to salts that are well known in the art. For example, S. M Berge et al. describe pharmaceutically acceptable salts in detail in (J. Pharmaceutical Sciences, 66:1-19 (1977)). Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include nitrate, bisulfate, borate, formate, butyrate, valerate, 3-phenylpropionate, camphorate, adipate, benzoate, oleate, palmitate, stearate, laurate, lactate, fumarate, ascorbate, aspartate, nicotinate, p-toluenesulfonate, camphorsulfonate, methanesulfonate, 2-hydroxyethanesulfonate, gluconate, glucoheptonate, lactobionate, glycerophosphate,

pectinate, lauryl sulfate, and the like, metal salts such as sodium, potassium, magnesium or calcium salts or amino salts such as ammonium, triethylamine salts, and the like, all of which may be prepared according to conventional methods.

The term "pharmaceutically acceptable ester," as used herein, refers to esters of compounds of the present invention which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Examples of pharmaceutically acceptable, non-toxic esters of the present invention include C_1-to-C_6 alkyl esters and C_5-to-C_7 cycloalkyl esters, although C_1-to-C_4 alkyl esters are preferred. Esters of the compounds of formula I-VI may be prepared according to conventional methods.

The term "pharmaceutically acceptable amide," as used herein, refers to non-toxic amides of the present invention derived from ammonia, primary C_1-to-C_6 alkyl amines and secondary C_1-to-C_6 dialkyl amines. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-to-C_3 alkyl primary amides and C_1-to-C_2 dialkyl secondary amides are preferred. Amides of the compounds of formula I-VI may be prepared according to conventional methods. It is intended that amides of the present invention include amino acid and peptide derivatives of the compounds of formula I-VI, as well.

The term "pharmaceutically acceptable prodrug" or "prodrug," as used herein, represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use. Prodrugs of the present invention may be rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in (T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987)).

The term "prodrug ester group," as used herein refers, to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art. Other examples of prodrug ester groups can be found in the book ("Pro-drugs as Novel Delivery Systems," by Higuchi and Stella) cited above.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which can be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active compound(s) which is effective to achieve the desired therapeutic response for a particular patient, compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The present invention contemplates pharmaceutically active metabolites formed by in vivo biotransformation of compounds of formula I-VI. The term pharmaceutically active metabolite, as used herein, refers to a compound formed by the in vivo biotransformation of compounds of formula I-VI. The present invention contemplates compounds of formula I-VI and metabolites thereof. A thorough discussion of biotransformation is provided in Goodman and Gilman's, The Pharmacological Basis of Therapeutics, seventh edition, hereby incorporated by reference.

The compounds of the invention, including but not limited to those specified in the examples, possess potassium channel opening activity in mammals (especially humans). As potassium channel openers, the compounds of the present invention are useful for the

treatment and prevention of diseases such as asthma, epilepsy, hypertension, Raynaud's syndrome, impotence, migraine, pain, eating disorders, urinary incontinence, functional bowel disorders, neurodegeneration and stroke.

The ability of the compounds of the invention to treat asthma, epilepsy, hypertension, Raynaud's syndrome, male sexual dysfunction, female sexual dysfunction, migraine, pain, eating disorders, urinary incontinence, functional bowel disorders, neurodegeneration and stroke can be demonstrated according to the methods described (D. E. Nurse et al., Br. J. Urol., v. 68 pp. 27-31 (1991); B. B. Howe et al., J. Pharmacol. Exp. Ther., v. 274 pp. 884-890 (1995); K. Lawson, Pharmacol. Ther., v. 70 pp. 39-63 (1996); D. R. Gehlert, et al., Neuro-Psychopharmacol & Biol. Psychiat., v. 18 pp. 1093-1102 (1994); M. Gopalakrishnan et al., Drug Development Research, v. 28 pp. 95-127 (1993); J.E. Freedman et al., The Neuroscientist, v. 2 pp. 145-152 (1996); D. Spanswick et al., Nature, v. 390 pp. 521-25 (December 4, 1997)).

Aqueous liquid compositions of the present invention are particularly useful for the treatment and prevention of asthma, epilepsy, hypertension, Raynaud's syndrome, male sexual dysfunction, female sexual dysfunction, migraine, pain, eating disorders, urinary incontinence, functional bowel disorders, neurodegeneration and stroke.

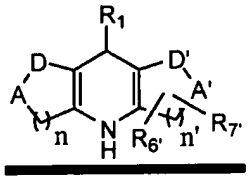
When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, amide or prodrug form. Alternatively, the compound can be administered as a pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically acceptable excipients. The phrase "therapeutically effective amount" of the compound of the invention means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age,

body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.003 to about 10 mg/kg/day. For purposes of oral administration, more preferable doses can be in the range of from about 0.01 to about 5 mg/kg/day. If desired, the effective daily dose can be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

WE CLAIM:

1. A compound having formula I



I,

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof, wherein

n and n' are independently 1-3;

A is selected from the group consisting of O, $-NR_2$, and S;

A' is selected from the group consisting of O, $-NR_{2'}$, S, and $CR_{4'}R_{5'}$;

D is selected from the group consisting of CH_2 and C(O);

D' is selected from the group consisting of CH_2, C(O), S(O), and $S(O)_2$;

R_1 is selected from the group consisting of aryl and heterocycle;

R_2 and $R_{2'}$ are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, $-NZ_1Z_2$, and (NZ_1Z_2)alkyl wherein Z_1 and Z_2 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

$R_{4'}$ and $R_{5'}$ are independently selected from the group consisting of hydrogen and alkyl;

$R_{6'}$ and $R_{7'}$ are independently selected from the group consisting of hydrogen and alkyl;

with the proviso that when D is CH_2 then D' is other than CH_2;

with the proviso that when D' is S(O) or $S(O)_2$ then A' is $CR_{4'}R_{5'}$; and

with the proviso that the following compounds are excluded,

8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4- e]pyridine-2,6-dipropanoic acid,

(8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4- e]pyridine-2,6-ethyldipropanate,

8-[2-(difluoromethoxy)phenyl]-6-methyl-4,5,6,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,4-e]pyridine-1,7(3H)-dione,

8-[2-(difluoromethoxy)phenyl]-2,6-dimethyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

2,6-dimethyl-8-phenyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

8-(3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2,4-dichlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-methoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-iodophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-phenyl-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-aminophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[2-(difluoromethoxy)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2,3,4-trimethoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[2-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-chloro-3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

3,7-dimethyl-10-phenyl-3,4,5,6,7,10-hexahydro-1H,9H-dipyrano[4,3-b:3,4-e]pyridine-1,9-dione,

6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(1,3-benzodioxol-5-yl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

9-(3-methoxyphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

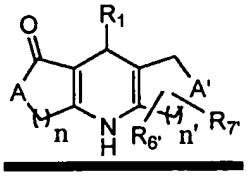
9-(2-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

6,6-dimethyl-9-(2-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

6,6-dimethyl-9-[2-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione, and

9-[3-(benzyloxy)phenyl]-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione.

2. A compound according to claim 1 of formula II



II,

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof wherein,

n and n' are independently 1-3;

A is selected from the group consisting of O, -NR_2, and S;

A' is selected from the group consisting of O, -$NR_{2'}$, S, and $CR_4R_{5'}$;

R_1 is selected from the group consisting of aryl and heterocycle;

R_2 and $R_{2'}$ are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, -NZ_1Z_2, and (NZ_1Z_2)alkyl wherein Z_1 and Z_2 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

$R_{4'}$ and $R_{5'}$ are independently selected from the group consisting of hydrogen and alkyl; and

$R_{6'}$ and $R_{7'}$ are independently selected from the group consisting of hydrogen and alkyl.

3. A compound according to claim 2 wherein,

A is NR_2;

A' is $NR_{2'}$; and

n' is 1.

4. A compound according to claim 2 wherein,

A is NR_2;

A' is O; and

n' is 1.

5. A compound according to claim 2 wherein,

A is NR_2;

A' is S; and

n' is 1.

6. A compound according to claim 2 wherein,

A is NR_2;

A' is $CR_{4'}R_{5'}$; and

n' is 1.

7. A compound according to claim 2 wherein,

A is O;

A' is $NR_{2'}$; and

n' is 1.

8. A compound according to claim 2 wherein,
A is O;
A' is O; and
n' is 1.

9. A compound according to claim 2 wherein,
A is O;
A' is S; and
n' is 1.

10. A compound according to claim 2 wherein,
A is O;
A' is CR_4R_5; and
n' is 1.

11. A compound according to claim 2 wherein,
A is S;
A' is NR_7; and
n' is 1.

12. A compound according to claim 2 wherein,
A is S;
A' is O; and
n' is 1.

13. A compound according to claim 2 wherein,
A is S;
A' is S; and
n' is 1.

14. A compound according to claim 2 wherein,
A is S;
A' is $CR_{4'}R_{5'}$; and
n' is 1.

15. A compound according to claim 2 wherein,
A is NR_2;
A' is $NR_{2'}$; and
n' is 2.

16. A compound according to claim 2 wherein,
A is NR_2;
A' is O; and
n' is 2.

17. A compound according to claim 2 wherein,
A is NR_2;
A' is S; and
n' is 2.

18. A compound according to claim 2 wherein,
A is NR_2;
A' is $CR_{4'}R_{5'}$; and
n' is 2.

19. A compound according to claim 2 wherein,
A is O;
A' is $NR_{2'}$; and
n' is 2.

20. A compound according to claim 2 wherein,
A is O;
A' is O; and
n' is 2.

21. A compound according to claim 2 wherein,
A is O;
A' is S; and
n' is 2.

22. A compound according to claim 2 wherein,
A is O;
A' is $CR_{4'}R_{5'}$; and
n' is 2.

23. A compound according to claim 2 wherein,
A is S;
A' is $NR_{2'}$; and
n' is 2.

24. A compound according to claim 2 wherein,
A is S;
A' is O; and
n' is 2.

25. A compound according to claim 2 wherein,
A is S;
A' is S; and
n' is 2.

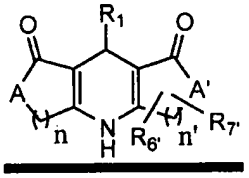
26. A compound according to claim 2 wherein,

A is S;

A' is $CR_{4'}R_{5'}$; and

n' is 2.

27. A compound according to claim 1 of formula III



III,

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof wherein,

n and n' are independently 1-3;

A is selected from the group consisting of O, $-NR_2$, and S;

A' is selected from the group consisting of O, $-NR_{2'}$, S, and $CR_{4'}R_{5'}$;

R_1 is selected from the group consisting of aryl and heterocycle;

R_2 and $R_{2'}$ are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, $-NZ_1Z_2$, and (NZ_1Z_2)alkyl wherein Z_1 and Z_2 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

$R_{4'}$ and $R_{5'}$ are independently selected from the group consisting of hydrogen and alkyl; and

$R_{6'}$ and $R_{7'}$ are independently selected from the group consisting of hydrogen and alkyl.

28. A compound according to claim 27 wherein,

A is NR_2;

A' is $NR_{2'}$; and

n' is 1.

29. A compound according to claim 27 wherein,
A is NR_2;
A' is $NR_{2'}$;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 1; and
n' is 1.

30. A compound according to claim 29 selected from the group consisting of
8-(3-bromo-4-fluorophenyl)-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione; and
8-(3-bromo-4-fluorophenyl)-2,6-dimethyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione.

31. A compound according to claim 27 wherein,
A is NR_2;
A' is O; and
n' is 1.

32. A compound according to claim 27 wherein
A is NR_2;
A' is O;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 1; and
n' is 1.

33. A compound according to claim 32 that is 8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,4-e]pyridine-1,7(3H)-dione.

34. A compound according to claim 27 wherein,
A is NR_2;
A' is S; and
n' is 1.

35. A compound according to claim 27 wherein,
A is NR_2;
A' is CR_4R_5; and
n' is 1.

36. A compound according to claim 27 wherein,
A is NR_2;
A' is CR_4R_5;
R_6 is hydrogen;
R_7 is hydrogen;
n is 1; and
n' is 1.

37. A compound according to claim 36 selected from the group consisting of
8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4- e]pyridine-1,7-dione,
8-(3-bromo-4-fluorophenyl)-2-ethyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4- e]pyridine-1,7-dione,
8-(3-bromo-4-fluorophenyl)-2-(2-methoxyethyl)-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione,
8-(3-bromo-4-fluorophenyl)-2-[2-(4-morpholinyl)ethyl]-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione hydrochloride,
8-(3-bromo-4-fluorophenyl)-2-[2-(dimethylamino)ethyl]-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione hydrochloride,

(8R)-8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione, and (8S)-8-(3-bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[b]pyrrolo[3,4-e]pyridine-1,7-dione.

38. A compound according to claim 27 wherein,
A is NR_2;
A' is $CR_{4'}R_{5'}$;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 2; and
n' is 1.

39. A compound according to claim 38 selected from the group consisting of
9-(3-bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,
9-(3-chloro-4-fluorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione
9-[4-fluoro-3-(trifluoromethyl)phenyl]-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,
9-(4-chloro-3-fluorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,
9-(3,4-dichlorophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,
9-[4-chloro-3-(trifluoromethyl)phenyl]-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,
9-(3,4-dibromophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,
9-(3-cyanophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(5-chloro-2-thienyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(3-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione,

9-(5-nitro-2-thienyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione, and

9-(5-nitro-3-thienyl)-3,4,5,6,7,9-hexahydro-1H-cyclopenta[b][1,6]naphthyridine-1,8(2H)-dione.

40. A compound according to claim 27 wherein,
A is O;
A' is $NR_{2'}$; and
n' is 1.

41. A compound according to claim 27 wherein,
A is O;
A' is O; and
n' is 1.

42. A compound according to claim 27 wherein,
A is O;
A' is O;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 1; and
n' is 1.

43. A compound according to claim 42 selected from the group consisting of
8-(3-bromo-4-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[4-fluoro-3-(2-furyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-[4-fluoro-3-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(3,4-dichlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(4-methyl-3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(3-chloro-4-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(3,4-dibromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(3-bromo-4-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-[4-chloro-3-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(4-bromo-3-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(4-fluoro-3-isopropenylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(3-iodo-4-methylphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dionep; and
8-[3-(2-furyl)-4-methylphenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione.

44. A compound according to claim 27 wherein,
A is O;
A' is S; and
n' is 1.

45. A compound according to claim 27 wherein,
A is O;
A' is $CR_{4'}R_{5'}$; and
n' is 1.

46. A compound according to claim 27 wherein,
A is O;
A' is $CR_{4'}R_{5'}$;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 1; and
n' is 1.

47. A compound according to claim 46 selected from the group consisting of
8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,
(8S)-8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,
(8R)-8-(3-bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,
(8S)-8-(4-methyl-3-nitrophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,
(8R)-8-(4-methyl-3-nitrophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,
(8S)-8-(3,4-dichlorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,
(8R)-8-(3,4-dichlorophenyl)-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione,
(8S)-8-[4-fluoro-3-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione, and

(8R)-8-[4-fluoro-3-(trifluoromethyl)phenyl]-4,5,6,8-tetrahydro-1H-cyclopenta[b]furo[3,4-e]pyridine-1,7(3H)-dione.

48. A compound according to claim 27 wherein,
A is O;
A' is $CR_{4'}R_{5'}$;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 2; and
n' is 1.

49. A compound according to claim 48 that is selected from the group consisting of
9-(3-bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydrocyclopenta[b]pyrano[3,4-e]pyridine-1,8-dione; and
9-[4-fluoro-3-(trifluoromethyl)phenyl]-3,4,5,6,7,9-hexahydrocyclopenta[b]pyrano[3,4- e]pyridine-1,8-dione.

50. A compound according to claim 27 wherein,
A is S;
A' is $NR_{2'}$; and
n' is 1.

51. A compound according to claim 27 wherein,
A is S;
A' is O; and
n' is 1.

52. A compound according to claim 27 wherein,
A is S;
A' is S; and
n' is 1.

53. A compound according to claim 27 wherein,
A is S;
A' is $CR_{4'}R_{5'}$; and
n' is 1.

54. A compound according to claim 27 wherein,
A is NR_2;
A' is $NR_{2'}$; and
n' is 2.

55. A compound according to claim 27 wherein,
A is NR_2;
A' is $NR_{2'}$;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 2; and
n' is 2.

56. A compound according to claim 55 that is 10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydropyrido[4,3-b][1,6]naphthyridine-1,9(2H,5H)-dione.

57. A compound according to claim 27 wherein,
A is NR_2;
A' is O; and
n' is 2.

58. A compound according to claim 27 wherein,
A is NR_2;
A' is S; and
n' is 2.

59. A compound according to claim 27 wherein,
A is NR_2;
A' is CR_4R_5; and
n' is 2.

60. A compound according to claim 27 wherein,
A is NR_2;
A' is CR_4R_5;
R_6 is hydrogen;
R_7 is hydrogen;
n is 1; and
n' is 2.

61. A compound according to claim 60 that is selected from the group consisting of
9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,
9-(3-bromo-4-fluorophenyl)-2-ethyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,
9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,
9-(3-bromo-4-fluorophenyl)-2-(2-methoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,
(9R)-9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9R)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

9-(3-cyanophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

9-(3-bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9R)-9-(3-bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

(9S)-9-(3-bromo-4-fluorophenyl)-2-cyclopropyl-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione,

2-(2-aminoethyl)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione, and

(9S)-2-(2-aminoethyl)-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b]quinoline-1,8(4H)-dione.

62. A compound according to claim 27 wherein,

A is NR_2;

A' is CR_4R_5;

R_6 is hydrogen;

R_7 is hydrogen;

n is 2; and

n' is 2.

63. A compound according to claim 62 that is 10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydrobenzo[b][1,6]naphthyridine-1,9(2H,5H)-dione.

64. A compound according to claim 27 wherein,
A is O;
A' is $NR_{2'}$; and
n' is 2.

65. A compound according to claim 27 wherein,
A is O;
A' is O; and
n' is 2.

66. A compound according to claim 27 wherein,
A is O;
A' is S; and
n' is 2.

67. A compound according to claim 27 wherein,
A is O;
A' is $CR_{4'}R_{5'}$; and
n' is 2.

68. A compound according to claim 27 wherein,
A is O;
A' is $CR_{4'}R_{5'}$;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 1; and
n' is 2.

69. A compound according to claim 27 wherein,
A is O;
A' is $CR_{4'}R_{5'}$;
$R_{4'}$ is hydrogen;
$R_{5'}$ is hydrogen;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 1; and
n' is 2.

70. A compound according to claim 69 selected from the group consisting of
9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9R)-9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9S)-9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9S)-9-(4-fluoro-3-iodophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9R)-9-(4-fluoro-3-iodophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9R)-9-(3-chloro-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
9-[4-fluoro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline 1,8(3H,4H)-dione,
9-(4-chloro-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9S)-9-[4-fluoro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,

(9R)-9-[4-fluoro-3-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9S)-9-(3,4-dibromophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9R)-9-(3,4-dibromophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9S)-9-(4-methyl-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9R)-9-(4-methyl-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9S)-9-(3,4-dichlorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9R)-9-(3,4-dichlorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9S)-9-(4-chloro-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9R)-9-(4-chloro-3-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9S)-9-(3,4-difluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9R)-9-(3,4-difluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
(9S)-9-(3-bromo-4-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione, and
(9R)-9-(3-bromo-4-methylphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione.

71. A compound according to claim 27 wherein,
A is O;
A' is CR_4R_5;

$R_{4'}$ is methyl;

$R_{5'}$ is methyl;

$R_{6'}$ is hydrogen;

$R_{7'}$ is hydrogen;

n is 1; and

n' is 2.

72. A compound according to claim 71 selected from the group consisting of (-) 9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione; and
(+) 9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione.

73. A compound according to claim 27 wherein,

A is O;

A' is $CR_{4'}R_{5'}$;

$R_{6'}$ is hydrogen;

$R_{7'}$ is hydrogen;

n is 2; and

n' is 2.

74. A compound according to claim 73 selected from the group consisting of 10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-1H-pyrano[4,3-b]quinoline-1,9(5H)-dione and
10-[4-fluoro-3-(trifluoromethyl)phenyl]-3,4,6,7,8,10-hexahydro-1H-pyrano[4,3-b]quinoline-1,9(5H)-dione.

75. A compound according to claim 27 wherein,

A is S;

A' is $NR_{2'}$; and

n' is 2.

76. A compound according to claim 27 wherein,

A is S;

A' is O; and

n' is 2.

77. A compound according to claim 27 wherein,

A is S;

A' is S; and

n' is 2.

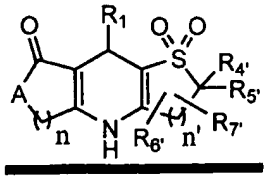
78. A compound according to claim 27 wherein,

A is S;

A' is $CR_{4'}R_{5'}$; and

n' is 2.

79. A compound according to claim 1 of formula IV



IV,

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof wherein,

n and n' are independently 1-3;

A is selected from the group consisting of O, $-NR_2$, and S;

R_1 is selected from the group consisting of aryl and heterocycle;

R_2 is selected from the group consisting of hydrogen, alkoxyalkyl, alkyl,

arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, -NZ_1Z_2, and (NZ_1Z_2)alkyl wherein Z_1 and Z_2 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

$R_{4'}$ and $R_{5'}$ are independently selected from the group consisting of hydrogen and alkyl; and

$R_{6'}$ and $R_{7'}$ are independently selected from the group consisting of hydrogen and alkyl.

80. A compound according to claim 79 wherein,

A is NR_2; and

n' is 1.

81. A compound according to claim 79 wherein,

A is NR_2;

$R_{6'}$ is hydrogen;

$R_{7'}$ is hydrogen;

n is 1; and

n' is 1.

82. A compound according to claim 81 that is 8-(3-bromo-4-fluorophenyl)-6-methyl-2,3,4,5,6,8-hexahydro-7H-pyrrolo[3,4-b]thieno[2,3-e]pyridin-7-one 1,1-dioxide.

83. A compound according to claim 79 wherein,

A is NR_2;

$R_{6'}$ is hydrogen;

$R_{7'}$ is hydrogen;

n is 2; and

n' is 1.

84. A compound according to claim 83 that is 9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-b][1,6]naphthyridin-8(4H)-one 1,1-dioxide.

85. A compound according to claim 79 wherein,
A is O; and
n' is 1.

86. A compound according to claim 79 wherein,
A is S; and
n' is 1.

87. A compound according to claim 79 wherein,
A is NR_2; and
n' is 2.

88. A compound according to claim 79 wherein,
A is NR_2;
$R_{6'}$ is hydrogen;
$R_{7'}$ is hydrogen;
n is 1; and
n' is 2.

89. A compound according to claim 88 that is 9-(3-bromo-4-fluorophenyl)-7-methyl-3,4,5,6,7,9-hexahydropyrrolo[3,4-b]thiopyrano[2,3-e]pyridin-8(2H)-one 1,1 dioxide.

90. A compound according to claim 79 wherein,
A is O; and
n' is 2.

91. A compound according to claim 79 wherein,

A is O;

$R_{6'}$ is hydrogen;

$R_{7'}$ is hydrogen;

n is 1; and

n' is 2.

92. A compound according to claim 91 that is selected from the group consisting of 9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide,

(9S)-9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide; and

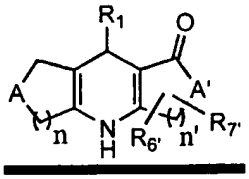
(9R)-9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2H-furo[3,4-b]thiopyrano[2,3-e]pyridin-8(5H)-one 1,1-dioxide.

93. A compound according to claim 79 wherein,

A is S; and

n' is 2.

94. A compound according to claim 1 of formula V



V,

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof wherein,

n and n' are independently 1-3;

A is selected from the group consisting of O, $-NR_2$, and S;

A' is selected from the group consisting of O, $-NR_{2'}$, S, and $CR_{4'}R_{5'}$;

R_1 is selected from the group consisting of aryl and heterocycle;

$R_{2'}$ and $R_{2'}$ are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, $-NZ_1Z_2$, and (NZ_1Z_2)alkyl wherein Z_1 and Z_2 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

$R_{4'}$ and $R_{5'}$ are independently selected from the group consisting of hydrogen and alkyl; and

$R_{6'}$ and $R_{7'}$ are independently selected from the group consisting of hydrogen and alkyl.

95. A compound according to claim 94 wherein,

A is NR_2;

A' is $NR_{2'}$; and

n' is 1.

96. A compound according to claim 94 wherein,

A is NR_2;

A' is O; and

n' is 1.

97. A compound according to claim 94 wherein,

A is NR_2;

A' is S; and

n' is 1.

98. A compound according to claim 94 wherein,

A is NR_2;

A' is $CR_{4'}R_{5'}$; and

n' is 1.

99. A compound according to claim 94 wherein,
A is O;
A' is $NR_{2'}$; and
n' is 1.

100. A compound according to claim 94 wherein,
A is O;
A' is O; and
n' is 1.

101. A compound according to claim 94 wherein,
A is O;
A' is S; and
n' is 1.

102. A compound according to claim 94 wherein,
A is O;
A' is $CR_{4'}R_{5'}$; and
n' is 1.

103. A compound according to claim 94 wherein,
A is S;
A' is $NR_{2'}$; and
n' is 1.

104. A compound according to claim 94 wherein,
A is S;
A' is O; and
n' is 1.

105. A compound according to claim 94 wherein,

A is S;

A' is S; and

n' is 1.

106. A compound according to claim 94 wherein,

A is S;

A' is $CR_{4'}R_{5'}$; and

n' is 1.

107. A compound according to claim 94 wherein,

A is NR_2;

A' is $NR_{2'}$; and

n' is 2.

108. A compound according to claim 94 wherein,

A is NR_2;

A' is O; and

n' is 2.

109. A compound according to claim 94 wherein,

A is NR_2;

A' is S; and

n' is 2.

110. A compound according to claim 94 wherein,

A is NR_2;

A' is $CR_{4'}R_{5'}$; and

n' is 2.

111. A compound according to claim 94 wherein,
A is O;
A' is $NR_{2'}$; and
n' is 2.

112. A compound according to claim 94 wherein,
A is O;
A' is O; and
n' is 2.

113. A compound according to claim 94 wherein,
A is O;
A' is S; and
n' is 2.

114. A compound according to claim 94 wherein,
A is O;
A' is $CR_{4'}R_{5'}$; and
n' is 2.

115. A compound according to claim 94 wherein,
A is S;
A' is $NR_{2'}$; and
n' is 2.

116. A compound according to claim 94 wherein,
A is S;
A' is O; and
n' is 2.

117. A compound according to claim 94 wherein,

A is S;

A' is S; and

n' is 2.

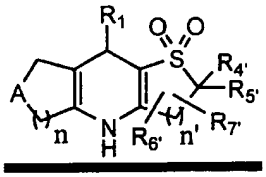
118. A compound according to claim 94 wherein,

A is S;

A' is $CR_{4'}R_{5'}$; and

n' is 2.

119. A compound according to claim 1 of formula VI



VI,

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof wherein,

n and n' are independently 1-3;

A is selected from the group consisting of O, $-NR_2$, and S;

R_1 is selected from the group consisting of aryl and heterocycle;

R_2 is selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, $-NZ_1Z_2$, and (NZ_1Z_2)alkyl wherein Z_1 and Z_2 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

$R_{4'}$ and $R_{5'}$ are independently selected from the group consisting of hydrogen and alkyl; and

$R_{6'}$ and $R_{7'}$ are independently selected from the group consisting of hydrogen and alkyl.

120. A compound according to claim 119 wherein,
A is NR_2; and
n' is 1.

121. A compound according to claim 119 wherein,
A is O; and
n' is 1.

122. A compound according to claim 119 wherein,
A is S; and
n' is 1.

123. A compound according to claim 119 wherein,
A is NR_2; and
n' is 2.

124. A compound according to claim 119 wherein,
A is O; and
n' is 2.

125. A compound according to claim 119 wherein,
A is S; and
n' is 2.

126. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

127. A method of treating asthma, epilepsy, Raynaud's syndrome, migraine, pain, eating disorders, functional bowel disorders, neurodegeneration and stroke by administering a compound of claim 1 including a compound selected from the

group consisting of 8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-2,6-dipropanoic acid, (8-[2-(difluoromethoxy)phenyl]-1,7-dioxo-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-2,6-ethyldipropanate, 8-[2-(difluoromethoxy)phenyl]-6-methyl-4,5,6,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,4-e]pyridine-1,7(3H)-dione, 8-[2-(difluoromethoxy)phenyl]-2,6-dimethyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

2,6-dimethyl-8-phenyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-b:3,4-e]pyridine-1,7-dione,

8-(3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2,4-dichlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-methoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-iodophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(3-bromophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-fluorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-phenyl-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-aminophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[2-(difluoromethoxy)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2,3,4-trimethoxyphenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-[2-(trifluoromethyl)phenyl]-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(2-chloro-3-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,

8-(4-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(3-chlorophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
8-(2-nitrophenyl)-5,8-dihydro-1H,3H-difuro[3,4-b:3,4-e]pyridine-1,7(4H)-dione,
3,7-dimethyl-10-phenyl-3,4,5,6,7,10-hexahydro-1H,9H-dipyrano[4,3-b:3,4-e]pyridine-1,9-dione,
6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
9-(1,3-benzodioxol-5-yl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
9-(3-methoxyphenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
9-(2-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
6,6-dimethyl-9-(2-nitrophenyl)-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione,
6,6-dimethyl-9-[2-(trifluoromethyl)phenyl]-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione; and
9-[3-(benzyloxy)phenyl]-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione.

128. The method of claim 128 for treating urinary incontinence.

129. The method of claim 128 for treating male erectile dysfunction and premature ejaculation.

130. The method of claim 128 for treating female anorgasmia, clitoral erectile insufficiency, vaginal engorgement, dyspareunia, and vaginismus.